School of Allied Health

Randomised, controlled trial of water-based exercise training in people with stable coronary heart disease

Anna Sarah Scheer

0000-0001-6348-7002

This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

March 2024

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Royal Perth Hospital Human Research Ethics Committee (EC00270), Approval number #REG15-165 (migrated reference RGS0000002071). Reciprocal ethical approval was provided by the Curtin University Human Research Ethics Committee (EC00262), Approval Number #HR227/2015 and the University of Western Australia Human Research Ethics Committee (EC00272), Approval Number #RA/4/1/8382.

Signature:

Anna Scheer

Date: 10.03.2024

Acknowledgement of Country

We acknowledge that Curtin University works across hundreds of traditional lands and custodial groups in Australia, and with First Nations people around the globe. We wish to pay our deepest respects to their ancestors and members of their communities, past, present, and to their emerging leaders. Our passion and commitment to work with all Australians and peoples from across the world, including our First Nations peoples are at the core of the work we do, reflective of our institutions' values and commitment to our role as leaders in the Reconciliation space in Australia.

Funding Disclosure

The candidate, Anna Scheer, was supported by an Australian Government Research Training Program (RTP) Scholarship and a Curtin University Postgraduate Research Scholarship.

Costs associated with the study were supported by a National Heart Foundation of Australia Vanguard Grant [grant number 101489] and a Spinnaker Health Research Foundation Grant (2017).

Publications and Presentations

Research papers related to thesis:

1. **Scheer AS**, Shah A, Ito Ramos de Oliveira B, Moreno-Suarez I, Jacques A, Green D, and Maiorana A. Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial. Journal of Physiotherapy 67: 284-290, 2021.

2. **Scheer AS**, Ito Ramos De Oliveira B, Shah A, Jacques A, Chasland LC, Green DJ, and Maiorana AJ. The effects of water-based circuit exercise training on vascular function in people with coronary heart disease. American Journal of Physiology-Heart and Circulatory Physiology 325: H1386-H1393, 2023.

3. **Scheer AS**, Maiorana A, Smith K, Carter H, Jacques A, Thomas H, Ito Ramos de Oliveira B, Green DJ. The effects of water-based circuit training exercise on cerebrovascular function in people with stable coronary heart disease. Journal of Physiology [submitted for review].

Conference papers related to thesis:

1. **Scheer AS**, Shah A, de Oliveira BIR, Green DJ, and Maiorana AJ. Water-based exercise training for coronary heart disease: 3119 May 29 4:30 PM - 4:45 PM. Med Sci Sports Exerc 52: 856-856, 2020.

2. Maiorana A, **Scheer AS**, Ramos de Oliveira B, Shah A, Jacques A, Moreno Suarez J, and Green D. Aquatic exercise in patients with stable coronary heart disease: A randomised, controlled trial. Heart Lung Circ 30: S275, 2021.

Selected conference presentations and workshops related to thesis:

1. Australian Physiotherapy Association ‘Ignite’ Conference October 2023., *Aquatic exercise training for coronary heart disease and type 2 diabetes*, Oral presentation, **Scheer AS**, IR de Oliveira B, Shah A, Green D.J., Maiorana A. (Keynote Speaker)

2. Australian Physiotherapy Association ‘Ignite’ Pre-Conference Workshop October 2023. *Aquatic aerobic and resistance exercise training for adults*, Invited Workshop, **Scheer AS**.

3. Australian Cardiovascular Health and Rehabilitation Association Annual Scientific Meeting July 2023, *Effects of water-based circuit exercise training on cerebrovascular outcomes in stable coronary heart disease*, Oral Presentation, **Scheer AS**, Maiorana A, de Oliveira BIR, Shah A, Green D.

4. Curtin University-School of Physiotherapy and Exercise Science Emerging Research Conference, November 2020, *Aquatic exercise for coronary heart disease*, Oral Presentation, **Scheer AS**, Shah A, de Oliveira BIR, Green D, Maiorana A. Exercise and Sports Science Australia Prize.

5. Australian Cardiovascular Health and Rehabilitation Association Annual Scientific Virtual Meeting, August 2020, *Aquatic exercise for stable coronary heart disease*, Oral Presentation, **Scheer AS**, Shah A, de Oliveira BIR, Green D, Maiorana A.

6. American College of Sports Medicine ASM 2020, May 2020, San Francisco, America, *Water-based exercise training for coronary heart disease*, Oral Presentation, **Scheer AS,** Shah A, de Oliveira BIR, Green D, Maiorana A. Cancelled due to COVID-19, narrated poster provided for the Virtual Experience.

7. Exercise and Sports Science Australia- Research to Practice 2020 Conference, April 2020, Perth, Australia, *Effects of Aquatic circuit training in people with coronary heart disease*, Poster, **Scheer AS**, Shah A, de Oliveira BIR, Green D, Maiorana A. **Delayed to March 2021 due to COVID-19, Online Poster.

8. South Metropolitan Health Service- Research Showcase 3 Minute Project Competition, November 2019, Perth, Australia, *Water-based exercise training for patients with coronary heart disease*, Oral Presentation, **Scheer AS**. Runner-up.

9. Australian Cardiovascular Health and Rehabilitation Association Annual Scientific Meeting August 2019, Sydney, Australia, *Fitness, fatness and artery function in coronary heart disease*, Oral Presentation, **Scheer AS**, Naylor L, Shah A, Ito Ramos de Oliveira B, Green D, Maiorana A.

10. Australian Cardiovascular Health and Rehabilitation Association Western Australia, Research Symposium, July 2019, Perth, Australia, *Fitness, fatness and artery function in coronary heart disease*, Oral Presentation, **Scheer AS**, Naylor L, Shah A, Ito Ramos de Oliveira B, Green D, Maiorana A.

Other publications during candidature:

1. Dorje T, Zhao G, **Scheer AS**, Tsokey L, Wang J, Chen Y, Tso K, Tan BK, Ge J, and Maiorana A. SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol. BMJ Open 2018;8(6):e021908.

2. Dorje T, Zhao G, Tso K, Wang J, Chen Y, Tsokey L, Tan BK, **Scheer AS**, Jacques A, Li Z, Wang R, Chow CK, Ge J, and Maiorana A. Smartphone and social media-based cardiac rehabilitation and secondary prevention in China (SMART-CR/SP): a parallel-group, single-blind, randomised controlled trial. Lancet Digit Health 2019;1(7):e363-e374.

3. Smith KJ, Moreno-Suarez I, **Scheer AS**, Dembo L, Naylor LH, Maiorana AJ, and Green DJ. Cerebral blood flow responses to exercise are enhanced in left ventricular assist device patients after an exercise rehabilitation program. J Appl Physiol. 2019;128(1): 108-116.

4. Smith KJ, Suarez IM, **Scheer AS**, Chasland LC, Thomas HJ, Correia MA, Dembo LG, Naylor LH, Maiorana AJ, and Green DJ. Cerebral blood flow during exercise in heart failure: Effect of Ventricular Assist Devices. Med Sci Sports Exerc. 2019;51(7): 1372-1379.

5. Wheeler MJ, Dunstan DW, Smith B, Smith KJ, **Scheer AS**, Lewis J, Naylor LH, Heinonen I, Ellis KA, Cerin E, Ainslie PN, and Green DJ. Morning exercise mitigates the impact of prolonged sitting on cerebral blood flow in older adults. J Appl Physiol. 2019;126(4): 1049-1055.

6. Moreno-Suarez I, **Scheer AS**, Lam K, Dembo L, Spence AL, Hayward C, Kaye DM, Leet A, Fuller LM, Jacques A, Naylor LH, Green DJ, and Maiorana A. High-intensity interval training in patients with left ventricular assist devices: A pilot randomized controlled trial. J Heart Lung Transplant. 2020;39(12):1380-1388.

7. **Scheer AS**, Naylor LH, Gan SK, Charlesworth J, Benjanuvatra N, Green DJ, and Maiorana AJ. The effects of water-based exercise training in people with type 2 diabetes. Med Sci Sports Exerc. 2020;52(2): 417-424.

Abstract

Background:

Coronary heart disease (CHD) is a leading cause of death and disease burden globally. Survival rates have improved over the last 30 years, however this leaves a large number of people living with CHD as a chronic condition. Combined aerobic and resistance exercise programs and ongoing habitual physical activity are part of current secondary prevention and cardiac rehabilitation guidelines, due to their association with improved functional outcomes, risk factors and survival in people with CHD. In addition to survival benefits, exercise training has been associated with improved aerobic fitness, muscular strength, traditional risk factors (such as blood pressure and lipid profile), cognition and vascular endothelial function. Despite the benefits of regular exercise, the uptake of exercise programs and maintenance of an active lifestyle is often sub-optimal in those with CHD. There are many reasons contributing to this, including time pressures, lack of motivation and health factors, such as musculoskeletal comorbidities, and falls risk. New, effective exercise programs that address these factors are needed to involve patients in ongoing, regular exercise. Water-based exercise is an option that may help to address these factors, through providing an option that minimises the load on the lower limb joints and spine and provides a low risk of harm from falling. Additionally, a water-based environment may cater to some patients' interests, and providing an individualised program with input from the patient is a key concept discussed in guidelines for exercise prescription for people with CHD.

The physical properties of water immersion make water-based exercise a promising alternative to gym-based exercise, which has typically been prescribed in patients with CHD. The buoyancy effect of water reduces the weight bearing load through the lower limb joints and spine, which may be beneficial to the approximately 60% of people with CHD who have comorbid musculoskeletal pathology, such as arthritis. Additionally, the hydrostatic pressure and thermal effects of exercising in warm water may increase peripheral blood flow and associated arterial shear stress, a key mediator of vascular endothelial adaptations. Improving vascular endothelial function is associated with improved survival in people with CHD, so determining if water-based exercise has beneficial effects on vascular function is of significant clinical importance. Furthermore, increased cerebral artery blood velocity has been observed during water-based exercise, compared to matched-intensity land-based

exercise, in young, healthy people. Whether this translates into training benefits for cerebrovascular function or cognitive outcomes in people with CHD has not previously been investigated.

Aims and hypotheses:

The overall aim of the trial was to determine whether water-based exercise training is an appropriate form of exercise, compared to gym-based exercise training for people with stable CHD. This was investigated through the following hypotheses:

1. Water-based circuit training exercise (WEX) and gym-based circuit training exercise (GEX) will both increase VO_{2peak} in people with stable CHD, and there will be no difference between modalities.
2. WEX and GEX will provide similar benefits to secondary outcomes, including muscular strength, body composition, blood profiles (lipid profile, inflammatory markers) and blood pressure.
3. WEX will improve endothelial function (measured as flow mediated dilation of the brachial artery) and cerebrovascular function.

Methods:

This was a randomised controlled trial of WEX versus GEX in people with CHD who were at least 6 months after a coronary event or intervention, and taking stable medications for at least one month. After undergoing baseline assessments, participants were randomised to 12 weeks of: i) WEX three times per week, for approximately one hour per session, ii) GEX three times per week for approximately one hour per session, or iii) a control group who continued their usual activities. Baseline assessments were repeated following the intervention period. Generalised linear mixed models with appropriate links were used for statistical analysis for within group pre-post assessment and group-time interactions.

Outcomes included:

- Aerobic capacity (cardiopulmonary exercise test, peak oxygen consumption [VO_{2peak}])
- Skeletal muscle strength (one repetition maximum [1RM]: of leg press, hamstring curl, bicep curl and latissimus dorsi pulldown)
- Anthropometry (weight, height, body mass index, waist and hip circumferences)

- Body composition (dual energy x-ray absorptiometry: fat mass, fat percentage, lean mass)
- Blood profiles (lipid profile, C-reactive protein, fibrinogen, renal function)
- Vascular endothelial function of the brachial artery (flow mediated dilation [FMD])
- Vascular endothelium independent function of the brachial artery (glyceryl trinitrate [GTN] mediated dilation)
- Resting blood pressure (automated blood pressure assessment)
- Cerebrovascular measures: cerebral artery blood velocity (resting middle and posterior cerebral artery velocity [MCAv and PCAv]), dynamic cerebral autoregulation (response of the MCAv to spontaneous and induced blood pressure oscillations, indicative of the brain's ability to buffer changes in systemic blood pressure), and neurovascular coupling (PCAv change in response to a visual stimulus).

Results:

Sixty participants underwent baseline assessments and 52 were randomised to the study (n=20 WEX, n=20 GEX, n=12 control). Forty-five participants completed the intervention (n=15 WEX, n=18 GEX, n=12 control). A sub-set of participants completed cerebrovascular or blood pressure assessments (n=11 WEX, n=14 GEX, n=10 control). Exercise training was well tolerated, with no adverse events with WEX, and one adverse event with GEX (an episode of supraventricular tachycardia in a person with a history of this condition, which resolved with medication). Data are presented as estimated mean and 95% confidence interval (CI).

Hypothesis 1: Aerobic capacity:

Compared to the control group, WEX and GEX improved aerobic capacity (WEX: +2.5ml.kg^{-1}.min^{-1}, 95% CI 0.6 to 4.4 ml.kg^{-1}.min^{-1}; GEX: +2.3 ml.kg^{-1}.min^{-1}, 95% CI 0.6 to 4.0 ml.kg^{-1}.min^{-1}), with no difference between WEX and GEX (WEX minus GEX:0.2 ml.kg^{-1}.min^{-1}, 95% CI -1.5 to 1.9 ml.kg^{-1}.min^{-1}).

Hypothesis 2: Traditional risk factors and training outcomes:

Compared to the control group, WEX and GEX improved hamstring curl strength (WEX: +6.3kg, 95% CI 1.2 to 11.3kg; GEX: +7.6kg, 95% CI 2.9 to 12.2kg) to a similar extent (WEX minus GEX: -1.3kg, 95% CI -5.8 to 3.2kg). WEX increased leg press strength ~7%

over time, but this was not significant compared to the change in the control group (WEX minus control: +7.1kg, 95% CI –3.5 to 17.7kg). GEX significantly improved leg press and latissimus dorsi pulldown strength compared to the control group (+15.5kg, 95% CI 5.7 to 25.3kg and +4.2kg, 95% CI 0.3 to 8.1kg, respectively) and bicep curl strength compared to WEX (+1.0kg, 95% CI 0.1 to 2.0kg). Reductions in fat mass, compared to the control group, were similar between training groups (WEX: -1.1kg, 95% CI -2.3 to 0.0kg; GEX: -1.2kg 95% CI -2.3 to -0.1kg). The only change in the lipid profile was a reduction in triglycerides in GEX (-0.16 $mmol.L^{-1}$, 95% CI -0.30 to -0.02 $mmol.L^{-1}$). Diastolic and mean arterial blood pressures demonstrated a tendency to reduce in the WEX group (DBP: -4mmHg, 95% CI -8mmHg to 0mmHg; MAP: -4mmHg 95% CI -9mmHg, to 0mmHg), with no between group differences observed.

Hypothesis 3: Peripheral and cerebrovascular responses:

Endothelial function (FMD) increased over time with WEX (1.3%, 95% CI 0.2 to 2.3%) but was stable following GEX and control. There were no changes in endothelium independent function for any group. There were no changes in resting cerebral blood velocities, conductance, or responses to a visual stimulus (neurovascular coupling). A difference was observed in the dynamic cerebral autoregulation responses between WEX and GEX. Very low frequency spectrum gain and normalised gain were lower with WEX than GEX at rest (gain: -0.35 $cm.s^{-1}.mmHg^{-1}$, 95% CI -0.62 to -0.09 $cm.s^{-1}.mmHg^{-1}$; normalised gain: -0.57 $cm.s^{-1}.mmHg^{-1}$, 95% CI-1.13 to -0.01 $cm.s^{-1}.mmHg^{-1}$) and during squat stands (gain: -0.33 $cm.s^{-1}.mmHg^{-1}$,95% CI -0.55 to -0.11 $cm.s^{-1}.mmHg^{-1}$; normalised gain: -0.51 $cm.s^{-1}.mmHg^{-1}$, 95% CI -0.76 to -0.26 $cm.s^{-1}.mmHg^{-1}$).

Conclusion:

WEX was well tolerated and there were no significant adverse events related to this modality. The first hypothesis that WEX would produce a similar increase in VO_{2peak} to GEX was supported by this research. The second hypothesis that WEX would provide similar improvements to strength, body composition, blood profiles and blood pressures was largely supported by this research, as both modalities improved hamstring strength and body fat, while GEX improved triglycerides and WEX demonstrated a tendency to reduce diastolic and mean arterial blood pressure. The third hypothesis was partially supported by this research: while WEX was the only group to demonstrate an improvement in endothelial function (assessed though brachial artery FMD) over time, this was not significantly greater than the change in the GEX cohort. Additionally, while WEX demonstrated improved

dynamic cerebral autoregulation measures compared to GEX, there were no significant changes in resting cerebral blood velocity outcomes in any cohort.

The clinical implication of these findings is that WEX can be considered as an effective alternative form of exercise training for people with stable CHD. The addition of WEX as an effective exercise option for people with CHD may help to engage a greater number of people with CHD in exercise, particularly those with musculoskeletal comorbidities who may have difficulty or pain with land-based training. These findings should encourage further research into WEX for improving cerebrovascular health, as well as the implementation of WEX into cardiac rehabilitation and secondary prevention programs.

Table of Contents

List of Figures

List of Tables

Abbreviations

CHD	Coronary heart disease
MI	Myocardial infarction
CR	Cardiac rehabilitation
$VO_{2[peak]}$	Oxygen consumption [peak oxygen consumption]
CVD	Cardiovascular disease
FMD	Flow mediated dilation
MCA[v]	Middle cerebral artery [velocity]
PCA[v]	Posterior cerebral artery [velocity]
WEX	Water-based aerobic and resistance circuit training exercise
GEX	Gym-based aerobic and resistance circuit training exercise
1RM	One repetition maximum
DXA	Dual energy x-ray absorptiometry
TCD	Transcranial Doppler ultrasound
ACS	Acute coronary syndrome
STEMI	ST segment elevated myocardial infarction
ECG	Electrocardiogram
NSTEMI	Non-ST segment elevation myocardial infarction
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
95% CI	95% confidence interval
COVID-19	Novel coronavirus 2019
YLD	Years lived with disability
USD	United States dollar
OR	Odds ratio
MET/S	Metabolic equivalent/s
SBP	Systolic arterial blood pressure
DBP	Diastolic arterial blood pressure
LDL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
BMI	Body mass index
UK	United Kingdom
CKD	Chronic kidney disease

CRP	C-reactive protein
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft
ACE	Angiotensin-converting enzyme
FITT [VP]	Frequency, intensity, type, time, [volume and progression]
P	Hydrostatic pressure
g	Gravity
ρ	Water density
h	Height
F_d	Drag force
C_d	Drag coefficient
v	Velocity
A	Frontal area of body
Tx	Thoracic
WOB	Work of breathing
VC	Vital capacity
ERV	Expiratory reserve volume
FRC	Functional residual capacity
ANP	Atrial natriuretic peptide
PRA	Plasma renin activity
NE	Norepinephrine
AVP	Arginine vasopressin
BF	Blood flow
EDV	End diastolic volume
BSA	Body surface area
CTL	Control group
NYHA	New York Heart Association
CHF	Chronic heart failure
HR	Heart rate
MAP	Mean arterial blood pressure
SV/SVI	Stroke volume/ stroke volume index
CO/CI	Cardiac output/ cardiac index
SVR	Systemic vascular resistance
TPR	Total peripheral resistance
$P_{ET}CO_2$	End tidal carbon dioxide

SNS	Sympathetic nervous system
PNS	Parasympathetic nervous system
MSNA	Muscle sympathetic nerve activity
HRV	Heart rate variability
RPE	Rating of perceived exertion
VCO_2	Carbon dioxide output
V_E/ VCO_2	Ventilatory equivalent for carbon dioxide
RER	Respiratory exchange ratio
BMD	Bone mineral density
GLMM	generalised linear mixed models
GTN	Glyceryl trinitrate/ glyceryl trinitrate mediated
Hx	History of
T2DM	Type 2 diabetes mellitus
CVA	Cerebrovascular accident (stroke)
TIA	Transient ischaemic attack
AUC	Area under the curve
eGFR	Estimated glomerular filtration rate
ALT	Alanine aminotransferase
ALK	Alkaline phosphatase
GGT	Gamma glutamyl transferase
CBFv/ CBv	Cerebral blood flow velocity / cerebral blood velocity
dCA	Dynamic cerebral autoregulation
NVC	Neurovascular coupling
AU	Arbitrary units
PI	Pulsatility index
CVCi	Cerebrovascular conductance index
nGain	Normalised gain
PR	Pulse ratio
CrCP	Critical closing pressure
RAP	Resistance area product

Glossary of Terms

Water-based circuit training exercise (WEX)	Alternating, short duration (45 second), stations of water-based aerobic and resistance exercises, conducted as a circuit with 15 seconds of active recovery between stations.
Gym-based circuit training exercise (GEX)	Alternating, short duration (45 second), stations of gym-based aerobic and resistance exercises, conducted as a circuit with 15 seconds of active recovery between stations.
Aerobic capacity	The peak oxygen uptake (VO_{2peak}) achieved during an exercise test to volitional exhaustion or medical termination.
Flow mediated dilation	An assessment of vascular endothelial function that utilises ultrasound to assess the ability of an artery to respond (increase diameter) to an increase in shear stress. The increase in shear stress is elicited by increasing blood flow, achieved through releasing a distal supra-systolic blood pressure cuff after a 5-minute inflation period.
Physical activity	Movement performed by skeletal muscles that increases energy expenditure.
Exercise	Physical activity performed with the intent of sustaining or improving fitness.
Cardiac rehabilitation	The collective multidisciplinary interventions aimed at assisting a person with cardiovascular disease to manage their condition through improving health behaviours, with the goal of maintaining or improving their function, and slowing or reversing disease progression.
Secondary prevention	Secondary prevention refers to health care targeted at preventing future cardiovascular events or complications in people with coronary heart disease.

List of Awards and Research Grants

Awards and scholarships:

2015

- Australian Postgraduate Award (Australian Government Research Training Program Scholarship)
- Curtin University Postgraduate Research Scholarship

2016

- Finalist, Curtin University 3 Minute Thesis competition
- Best Paper Presentation, Mark Liveris Seminar, Curtin University

2017

- Best New Presenter- Aquatic, Australian Physiotherapy Association conference
- Best Paper Presentation, Mark Liveris Seminar, Curtin University

2019

- Runner up, 3 Minute Project Competition, South Metropolitan Health Service, Perth

2020

- Exercise and Sports Science Australia Prize, Curtin University-School of Physiotherapy and Exercise Science Emerging Research Conference

Grants:

1. Chief Investigator: Maiorana A, Associate Investigators: **Scheer A**, Green D, Shah A. 2017 Heart Foundation Vanguard Grant. A randomised, controlled trial of water-based exercise training for people with stable coronary heart disease. Amount $75,000 AUD.

2. Chief Investigators: Maiorana A, Green D, Shah A, Associate Investigator: **Scheer A**. 2017 Spinnaker Foundation Health Research Grant. A randomised, controlled trial of water-based exercise training for people with stable coronary heart disease. Amount: $15,000 AUD

Statement of Contributors

The candidate, Anna Scheer, was responsible for all aspects of the research presented in this thesis, including the design of the project, data collection, analysis and interpretation, and the reporting of results. Professor Andrew Maiorana (Curtin University School of Allied Health) was the primary supervisor and contributed to research design and development, data collection, interpretation, editing and revision of the thesis. Dr. Beatriz Ito Ramos de Oliveira was an associate supervisor (Curtin University School of Allied Health) and contributed to research design, interpretation, and editing. Winthrop Professor Daniel J. Green (the University of Western Australia, School of Human Sciences) was an external associate supervisor, and contributed to research design, data interpretation and manuscript revision.

Dr. Amit Shah (Fiona Stanley Hospital) provided cardiology oversight for the trial. Ms. Angela Jaques (University of Notre Dame, Institute for Health Research) provided assistance with the design and interpretation of the statistical analysis. Dr. Kurt Smith assisted with the design of the cerebrovascular outcome assessment session and the interpretation of cerebrovascular outcome measures and Dr. Howard Carter assisted with advice on data processing for cerebrovascular outcomes.

Ms. Leanne Campbell assisted with aerobic capacity assessments and training sessions, Dr. Lauren Chasland assisted with some vascular function assessments and training sessions, Dr. José Ignacio Moreno-Suárez assisted with some muscular strength assessments and training sessions, and Dr. Hannah Thomas assisted with some cerebrovascular function assessments.

Editorial support:

I would like to thank and acknowledge Dr. Kathy Stiller for providing proof reading services for this thesis.

Acknowledgements

I finally get to complete this section of the thesis. It has been a (very) long journey to get here, and as such there are many people to thank and acknowledge. There have been many late nights and I've seen far too many sunrises over the last 9 years. Consequently, I've also discovered coffee. During this thesis I've gained two little people, crashed my bike, had a few surgeries and had some family not make it to the end of this journey with me. We've dealt with COVID, restrictions, what feels like 1,001 childhood illnesses, food intolerances and have had the ENT on speed dial. The team below have helped to get me through this and for that I'm eternally grateful.

My supervisors:

Andrew - Thank you for your advice, knowledge, and time over the course of this project and during my Honours before that. I am grateful for your patience with all of the other things life has thrown my way over the course of this thesis and for your support during these times.

Danny - I am very grateful for your help and support, for welcoming me into the lab group and allowing me to learn the skills I needed, while meeting an awesome group of researchers. Thank you for your time and patience!

Bea - Thank you for your help and time, for listening, reading my drafts, and for loaning me your pool for pilot work (and for getting in to help!). Melbourne is extremely lucky to get you!

Fiona Stanley Hospital staff:

I would like to thank Mr Eric Watson for his help with organising pool bookings and the water-based training sessions and Ms. Leanne Campbell for her assistance with training and testing sessions. A big thank you to the Cardiac Rehabilitation gym (especially Leanne, Tim and Fiona) and the Advanced Heart Failure and Cardiac Transplant Service staff for their support and the staff, particularly to Dr. Amit Shah for providing cardiology support for this project, the Fellows and cardiology residents for supervising exercise tests, Nicole for your friendship and answering all my administration questions and to Di for being there in the early hours during testing.

Other researchers and staff who assisted with trainings:

Thank you to Ms. Lucy Bolam, Dr. José Ignacio Moreno Suárez, Dr. Tashi Zhaxiduojie, Dr. Lauren Chasland and Ms. Shara Kinney for their assistance with training

sessions, as leave cover or second bodies, and Mr. Ray Davey for help handling changes to bookings while I was on leave.

Curtin School of Allied Health crew (past and present):

To Nacho and Tashi, who I started this journey with as fellow PhD students many years ago, thank you for your support and camaraderie. A big thank you for filling in as the 'second person' on the pool deck in the early hours of the morning when needed, and for providing leave cover for me for training group supervision or exercise assessments. Without statistical advice (and extreme patience) from Angela Jacques this project would have been so much more challenging, thank you for all you have taught me and for sharing your time, even after you left Curtin. Thank you to Prof. Luke Haseler for all for your support and guidance-it has meant a lot to me, and I am well and truly looking forward to moving on to new projects! Thank you to Prof. Kylie Hill for your help getting to the finishing line and to Di Hopper who helped me get into research many years ago.

UWA Cardiovascular Research Group (past and present):

What a lovely group of people! Thanks to you all for your support over the years, I have loved working with you, learning from you and having some fun too. To Lauren, Jaye, Elisa, Kurt and Howard- I feel like I have seen sunrise far too many times in the lab with you all - but the company made the early wake ups much easier! Thanks to Louise, Elisa, Andy, Kurt and Howard for showing me the ropes with the vascular and cerebrovascular assessments and for answering all my questions over the last few years. Thank you to Giovanna and Georgia for your help with car bays, administration and bookings, and thanks to Lou, Barb, Jaye and Julie for your advice and chats. I've seen a few fellow PhD students start and finish and have loved working alongside you all. To Hannah, Channa, Arga, Michael, Treya and Lucy thank you for making lab and uni life easier and brighter! There's a special mention to Lauren for embarking on mum/PhD life with me - I've loved watching T and H grow and I'm looking forward to 'less crazy' chapters of our lives! You and the TEX study gents in the gym made our training groups full of banter and fun. Finally, of course, thank you to Danny for heading up the team and guiding us.

Our research participants:

I would like to acknowledge the wonderful participants from the study, without whom this would not have been possible. Thank you for attending testing and training sessions and for making them enjoyable.

My family and friends:

To Dad- thank you for all of your support and help over the years, especially for letting Hugh and I move home for a bit when COVID first came, so I could study still when daycare was not an option. To my Aunt Heather - your support has been amazing over this journey, thank you so much. Tonia - thank you for answering all of the emergency kid questions and for your help throughout. Thank you also to Maryke, my lovely step-mum, who unfortunately didn't get to see this journey finished, and to Mum, who never got to see this journey started - though your passion for learning and all you taught me in my early years helped me get to where I am today.

To Hugh and Aurelia, thank you for your patience with me, for being dragged along to meetings at times (even at 2 weeks old), and for teaching me to enjoy the little pleasures in life and how to live with less sleep, which has come in handy these past months. Less of a thank you for the multitude of illnesses you bring home. In all seriousness, it has given me great joy watching you grow and become little people.

As it's often said – it takes a village - thank you to all of our wonderful friends, neighbours and team-mates for hanging in there for the journey and helping where you can, with practical or emotional support, I really appreciate it.

Finally, to my husband Jamie - thank you for putting up with the weird hours, for navigating parenthood with me and for your support with finishing this - even if you don't entirely know what I do.

Chapter 1. Introduction

This thesis contains six chapters, exploring water-based circuit training exercise (WEX) as an alternative modality for exercise training for people with stable coronary heart disease (CHD).

Chapter 1. Introduction.

Chapter 2. Literature review.

Chapter 3. The effects of WEX on aerobic fitness, strength and body composition in patients with stable CHD.

Chapter 4. The effects of WEX on vascular function and blood profiles in patients with stable CHD.

Chapter 5. The effects of WEX on cerebrovascular function in patients with stable CHD.

Chapter 6. Discussion and future directions.

1.1 Introduction

CHD is the result of a narrowing of the coronary arteries due to atherosclerosis (1). The risk of atherosclerosis increases when the vessel lining (the endothelium) becomes dysfunctional (1). A dysfunctional endothelium impairs the release of vasoactive substance, such as nitric oxide, that regulate vasodilation (2) and platelet aggregation (3) and allows lipids and other substances to accumulate inside the artery wall (1, 4). The sub-endothelial accumulations can progress from lipid rich macrophage ‘fatty streaks’ through to complex lesions with fibrous caps, and may develop necrotic cores or can calcify (1) and this perpetuates an inflammatory response (4). While atherosclerosis can occur throughout the arterial tree (5), it commonly presents in the coronary arteries where it can lead to a compromise in myocardial blood flow and perfusion (6, 7), leading to angina and myocardial infarction (MI) (7). MI refers to the death of myocardial cells resulting from prolonged ischaemia (8) and often occurs after an atherosclerotic plaque becomes unstable and ruptures, resulting in thrombus formation which can occlude a coronary artery (1).

CHD is a significant global issue, estimated to affect over 240 million people world-wide in 2020 (9), including over half a million Australians (10). Approximately 20,000 deaths

in Australia resulted from CHD in 2022, making it the leading cause of mortality (11). While survival from coronary events has significantly improved over the last 40 years (12, 13), in Australia the prevalence of CHD is much greater in older adults (10) and the overall population structure is aging (14). This highlights the need for effective cardiac rehabilitation (CR) and secondary prevention strategies, as increasing numbers of people are surviving with the CHD. Furthermore, the economic burden of CHD is substantial, costing Australia over $2 billion annually (15, 16).

Secondary prevention and CR programs target modifiable risk factors through lifestyle and behavioural measures, such as diet, smoking cessation and exercise, and aim to reduce the risk of recurrent coronary events (17, 18). One of the key risk factors for CHD is physical inactivity (19), which is estimated to contribute 11% of the burden of CHD in Australia (20). Consequently, regular exercise training and encouraging physical activity are core components of CR (21-24), with both aerobic and resistance exercise training recommended in current guidelines (22-24).

Exercise training in people with CHD has (25) been found to benefit aerobic capacity (26, 27), muscular strength (26, 28), cardiovascular risk factors (27, 29, 30), arterial function (31) and mortality outcomes (32). Increased aerobic capacity and higher levels of muscular strength have been associated with increased survival in people with CHD (33, 34). In a meta-analysis of 18 studies in people with CHD, exercise training resulted in a +2.3ml.kg^{-1}.min^{-1} improvement in peak oxygen uptake (VO_{2peak}) (35), the gold standard measure of aerobic capacity (36). Additionally, resistance training has been found to improve lower and upper body muscular strength by 25% and 46%, respectively (28) Further to this, exercise training and habitual physical activity in people with CHD have resulted in modest improvements in traditional cardiovascular risk profile factors, including lipid profiles (27), markers of inflammation (30), body composition (30) and blood pressure (27), when compared to sedentary individuals .

However, reduction in traditional risk factors fails to explain 40-60% of the benefit in cardiovascular risk reduction seen with exercise (37, 38). Improved vascular endothelial function from exercise has been hypothesised as contributing to this additional risk reduction (37). Endothelial dysfunction, a precursor to atherosclerosis, has been reported in people with CHD (39-42). Both peripheral and coronary artery endothelial function has been found to improve with exercise training in people with cardiovascular disease and diabetes (43-47).

Despite the mounting evidence supporting the benefit of exercise on cardiac and peripheral arteries, little is known about its effects on the cerebral circulation in people with CHD. Reduced cerebral blood flow velocity or reduced cerebral perfusion have been reported in people with CHD (48-50), and adverse changes to grey and white matter of the brain have also been observed (51-53). Furthermore, there is an increased risk of cognitive impairment or dementia in people with CHD (54). While exercise training has been shown to result in some improvement in regional cerebral perfusion (49), no changes have been observed in global measures of cerebral perfusion (50). Accordingly, further research into the effects of exercise training on cerebrovascular function and cognition are required.

Whilst the benefits of exercise on cardiovascular risk have been well established, adherence to long-term exercise is commonly sub-optimal, with less than half of coronary event survivors achieving sufficient levels of physical activity twelve months after an event (55, 56). Accordingly, new approaches are needed to facilitate long-term adherence to exercise.

Developing alternative exercise modalities to the typically prescribed gym-based or walking exercise programs may encourage more patients to exercise. Increased variety in exercise prescription is likely to cater for a wider range of patient preferences and address barriers to exercise participation, such as comorbidities like arthritis (57). Almost 60% of people with heart disease have reported musculoskeletal pain conditions or arthritis , and this sub-group of people with CVD were less likely to meet physical activity targets (57-59). Exercise modalities that reduce lower limb and spine weight bearing load, such as water-based exercise (60), may be particularly well suited to this cohort, if the same health benefits are evident.

Water immersion reduces weight bearing through the force of buoyancy acting upwards on the body equivalent to the amount of water the body has displaced (61). This depth-dependent response means a person submersed to the level of the xiphoid process only requires approximately 35% of their body weight to be transferred through their lower limbs and spine (62). This may be advantageous for the large sub-population of people with CHD who are overweight or obese, or have musculoskeletal pain conditions, such as arthritis. Lee, Joo and Brubaker (2020) recently found that six months of water walking provided similar benefit to land walking for changing body fat, cholesterol and aerobic capacity in people with CHD and arthritis (63).

Short-duration, high frequency (2-3 week, twice daily) programs of WEX in people with CHD have demonstrated improvements in VO_{2peak} and peak workload/power output (64-66), however these programs would be difficult to maintain as an ongoing program due to their high frequency. Longer duration (16-24 week) upright, water-based interventions in people with CHD (67-70) have consisted of either aerobic training only (67, 70), or aerobic and resistance training as separate training sessions (68, 69), with no studies examining aerobic and resistance circuit training, or even conducting both modalities within one session. Only two longer-duration studies have assessed VO_{2peak}, with water-based programs demonstrating increases over time (69, 70), however neither group provided a comparator to a standard gym-based training program with a resistance exercise component. Whole body strength was increased in water-based exercise programs that included resistance exercise (68, 69), although further research is needed to determine if water-based aerobic and resistance circuit training would provide similar benefits to muscular strength.

Water immersion also results in distinct haemodynamic responses which may translate to effects on the vasculature. The effect of hydrostatic pressure on the body increases venous return from the lower limbs, precipitating and approximately 700ml increase in the thoracic circulation (71). This has been found to augment cardiac diastolic volumes and preload in healthy individuals, resulting in increased stroke volume and cardiac output (71-74), while reducing peripheral vascular resistance (72, 74-77), a pattern also observed in people with CHD (78-80). In people with CHD, heart rate has been found to decrease (80, 81) or remain unchanged (82) with water immersion. In people with and without CHD, water-immersed exercise causes the same pattern of changes in cardiac output, stroke volume, heart rate and peripheral resistance seen with land-based exercise, but starting from the altered resting immersion values described above (75, 78-80, 83-85).

The vascular effects noted above may elicit an additional stimulus on the vascular endothelium, with increases in brachial artery (72) and forearm skeletal muscle blood flow (86) observed during thermoneutral (34-35°C) water immersion in healthy young adults. These effects appear to persist during exercise in healthy young adults, with increased brachial artery antegrade shear stress observed during underwater cycling exercise in 32 and 38 °C water immersed to the umbilicus (87). Shear stress is a known mediator of endothelial function (88), and increased shear stress during water-based exercise may be a mechanism for augmenting endothelial function.

Limited research has investigated whether these acute effects translate into training benefits for people with CHD. Three weeks of high-frequency land and water-based exercise training increased plasma nitrate levels (a metabolite of nitric oxide) compared to land-based exercise training alone in people with CHD (65) and flow mediated dilation (FMD), a measure of endothelial function, was increased after 2 weeks of intensive water-based training (66). While the Vasić et al. (2019) found land and water-based exercise training over 2 weeks similarly increased FMD, the authors acknowledged randomisation failure, and there was a large baseline difference in FMD (5.5% vs 7.2%) between the water and land-based groups (66). This may have impacted the between-group findings, as people with low FMD scores at baseline are more likely to increase FMD with training (89), highlighting the need for future research in this area. Indeed, in people with type 2 diabetes longer duration (12 week) studies of water-based exercise demonstrated greater change in FMD and microvascular function than land-based training (90, 91). Additionally, it is important to determine whether longer duration, less intensive water-based exercise programs can improve endothelial function in people with CHD, as twice daily training is unlikely to be sustainable for the majority of patients as an ongoing program.

The cerebral circulation also appears to be impacted acutely by changes in central blood volume and cardiac output during water immersion. Increases in middle and posterior cerebral artery blood flow velocity (MCAv and PCAv; surrogate measures of cerebral blood flow) and oxygenated haemoglobin have been observed with resting immersion in healthy individuals (92, 93), and the increases in MCAv and PCAv over non-immersion values have been maintained during exercise (83). However, little research has examined the effects of water-based exercise training on cerebrovascular function. In a six months study of water-walking in healthy older adults, there were no changes in resting MCAv (94), although dynamic cerebral autoregulation was improved with the water walking group, compared to the land walking group (94). Dynamic cerebral autoregulation describes the ability of the cerebrovasculature to buffer changes in systemic blood pressure to maintain a constant blood supply to the brain, such as during changes in position (95). Whether these effects occur in people with CHD remains to be determined.

In summary, exercise plays a significant role in secondary prevention strategies for people with stable CHD, yet less than 30% of people living with CHD are meeting physical activity guidelines (55, 96-99). An increase in the proportion of people with CHD who are attending exercise-based cardiac rehabilitation and adhering to secondary prevention strategies, such as regular exercise, is likely to reduce the prevalence of major adverse

cardiovascular events and the economic burden of CHD (100). Innovative exercise strategies, such as water-based exercise, may play a role in achieving this, if they are proven to provide comparable health and fitness benefits for patients as conventional gym-based approaches. Water-based exercise induces a reduced weight bearing load to the lower limbs and spine, which may encourage people with CHD and musculoskeletal complications to engage in exercise. Additionally, water-based exercise may be beneficial for very deconditioned patients, and those at risk of falls. Moreover, a broader range of exercise modalities will increase the variety of options available to patients, which may help to accommodate individual preferences and increase engagement with programs.

1.2 Research question and hypotheses

The gaps in the literature surrounding the efficacy of combined aerobic and resistance water-based exercise training for people with stable CHD in a sustainable, medium to longer duration format drives the primary research question:

Is water-based combined aerobic and resistance circuit training exercise (WEX) an appropriate form of exercise for people with stable CHD, when compared to combined aerobic and resistance gym-based circuit training exercise (GEX) and continuing usual activities (control)?

This will be examined through the following hypotheses:

1. WEX and GEX will both increase VO_{2peak} in people with stable CHD, and there will be no difference between modalities.
2. WEX and GEX will provide similar benefits to secondary outcomes including muscular strength, body composition, blood profiles (lipid profile, inflammatory markers) and blood pressure.
3. WEX will improve endothelial function (measured as flow mediated dilation of the brachial artery) and cerebrovascular function.

1.3 Thesis overview

This thesis presents the results of studies that investigated the effects of a combined aerobic and resistance circuit training exercise program conducted for one hour, three times per week for twelve weeks in people with stable CHD, either in a cardiac rehabilitation gymnasium, or a hydrotherapy pool, and these programs were compared to continuing usual

activities as a control group, in a randomised, controlled trial (see Figure 1.1). Training programs were matched for frequency, duration and intensity. Furthermore, resistance exercises were matched for muscle group between WEX and GEX. Assessments included the primary outcome measure of aerobic capacity (VO_{2peak}), with secondary outcome measures including muscular strength (one repetition maximum [1RM] assessments), body composition (anthropometric measurements, dual energy x-ray absorptiometry [DXA]), blood biomarkers (lipid profiles, liver and kidney function, inflammatory markers), blood pressure, cerebral blood flow (transcranial Doppler ultrasound [TCD] assessments) and brachial artery endothelium function and endothelium independent function (FMD and glyceryl trinitrate mediated function assessments) to establish if WEX is an appropriate form of exercise compared to GEX for people with stable CHD. Data collection for the studies presented in this thesis occurred between January 2017 and July 2019.

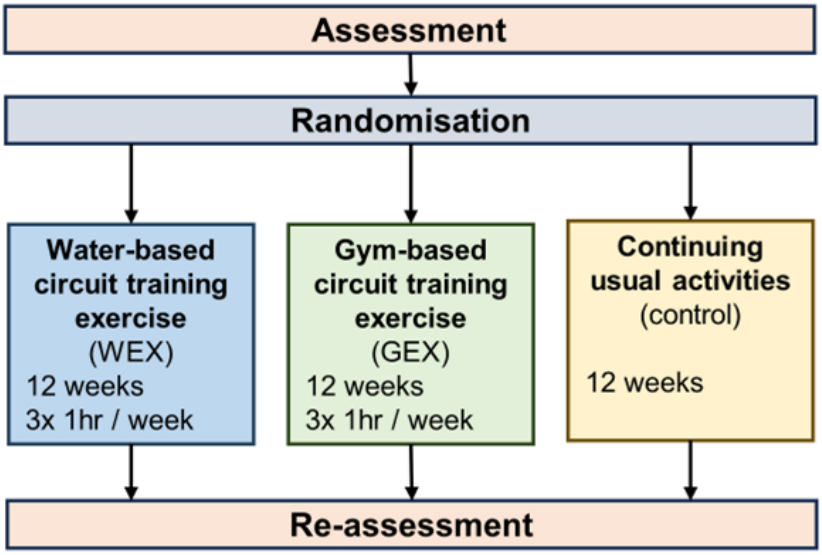


Figure 1.1 Study overview

Chapter 3 has been published as a manuscript in the Journal of Physiotherapy, Chapter 4 has been published as a manuscript in the American Journal of Physiology: Heart and Circulatory Physiology and Chapter 5 has been submitted as a manuscript to the Journal of Physiology.

1.4 References

1. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
2. Wray DW, Witman MA, Ives SJ, McDaniel J, Fjeldstad AS, Trinity JD, et al. Progressive handgrip exercise: evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. Am J Physiol Heart Circ Physiol. 2011;300(3):H1101-7.
3. Radomski MW, Palmer RMJ, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet. 1987;330(8567):1057-8.
4. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.
5. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, et al. Prevalence, vascular distribution and multi-territorial extent of subclinical atherosclerosis in a middle-aged cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. Circulation. 2015;131:2104-13.
6. Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. Nature. 2008;451(7181):953-7.
7. Falk E, Shah PK, De Feyter P. Ischaemic Heart Disease. London: Manson Publishing; 2009.
8. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237-69.
9. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: A report from the American Heart Association. Circulation. 2022;145(8):e153-e639.
10. Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts. Canberra: AIHW; 2023.
11. Australian Bureau of Statistics. Causes of Death, Australia 2022 Canberra: ABS; 2023 [Available from: https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/latest-release.]
12. Australian Institute of Health and Welfare. Trends in coronary heart disease mortality: age groups and populations. Canberra: AIHW; 2014.
13. Australian Institute of Health and Welfare. Cardiovascular disease snapshot 2018; Cat. no: CVD 83. Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/how-many-australians-have-cardiovascular-disease.
14. Australian Government Centre for Population. National population projections in the Intergenerational Report 2021, by broad age group, 2020-21 to 2060-61 Canberra: the Australian Government; 2021.
15. Australian Institute of Health and Welfare. Cardiovascular disease: Australian facts 2011. Canberra, Australian Capital Territory: AIHW; 2011.
16. Australian Institute of Health and Welfare. Health-care expenditure on cardiovascular diseases 2008–09. Canberra: AIHW; 2014.
17. National Heart Foundation of Australia, Australian Cardiac Rehabilitation Association. Recommended framework for cardiac rehabilitation '04: National Heart Foundation of Australia 2004.
18. National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: An expert guide to clinical practice for secondary prevention of coronary heart disease. Melbourne: National Heart Foundation of Australia 2012.
19. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
20. Australian Institute of Health Welfare. Impact of physical inactivity as a risk factor for chronic conditions: Australian burden of disease. Canberra: AIHW; 2017.
21. Woodruffe S, Neubeck L, Clark RA, Gray K, Ferry C, Finan J, et al. Australian Cardiovascular Health and Rehabilitation Association (ACRA) core components of cardiovascular disease secondary prevention and cardiac rehabilitation 2014. Heart Lung Circ. 2015;24(5):430-41.
22. Verdicchio C, Freene N, Hollings M, Maiorana A, Briffa T, Gallagher R, et al. A clinical guide for assessment and prescription of exercise and physical activity in cardiac rehabilitation. A CSANZ Position Statement. Heart Lung Circ. 2023; 32(9):1035-1048.
23. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. J Am Coll Cardiol. 2023;82(9):833-955.

24. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021;28(5):460-95.
25. Dibben GO, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler A-D, et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. Eur Heart J. 2023;44(6):452-69.
26. Fan Y, Yu M, Li J, Zhang H, Liu Q, Zhao L, et al. Efficacy and safety of resistance training for coronary heart disease rehabilitation: A systematic review of randomized controlled trials. Front Cardiovasc Med. 2021;8:754794.
27. Chen YC, Tsai JC, Liou YM, Chan P. Effectiveness of endurance exercise training in patients with coronary artery disease: A meta-analysis of randomised controlled trials. Eur J Cardiovasc Nurs. 2017;16(5):397-408.
28. Hollings M, Mavros Y, Freeston J, Fiatarone Singh M. The effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. Eur J Prev Cardiol. 2017;24(12):1242-59.
29. Theodorou AA, Panayiotou G, Volaklis KA, Douda HT, Paschalis V, Nikolaidis MG, et al. Aerobic, resistance and combined training and detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery disease patients. Res Sports Med. 2016;24(3):171-84.
30. Sjölin I, Bäck M, Nilsson L, Schiopu A, Leosdottir M. Association between attending exercise-based cardiac rehabilitation and cardiovascular risk factors at one-year post myocardial infarction. PLoS One. 2020;15(5):e0232772.
31. Manresa-Rocamora A, Ribeiro F, Casanova-Lizón A, Flatt AA, Sarabia JM, Moya-Ramón M. Cardiac rehabilitation improves endothelial function in coronary artery disease patients. Int J Sports Med. 2022;43(11):905-20.
32. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf M-I, Hackbusch M, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). Eur J Prev Cardiol. 2020;27(16):1756-74.
33. Kamiya K, Masuda T, Tanaka S, Hamazaki N, Matsue Y, Mezzani A, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. Am J Med. 2015;128(11):1212-9.
34. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, et al. Cardiac rehabilitation fitness changes and subsequent survival. Eur Heart J Qual Care Clin Outcomes. 2018;4(3):173-9.
35. Valkeinen H, Aaltonen S, Kujala UM. Effects of exercise training on oxygen uptake in coronary heart disease: a systematic review and meta-analysis. Scand J Med Sci Sports. 2010;20(4):545-55.
36. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, Dalleck LC. Graded exercise testing protocols for the determination of VO2max: Historical perspectives, progress, and future considerations. J Sports Med. 2016;2016:3968393.
37. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. J Physiol. 2009;587(Pt 23):5551-8.
38. Mora S, Md MHS, Cook N, Buring J, Ridker P, M Md MPH, et al. Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. Circulation. 2007;116(19):2110-8.
39. Agewall S, Henareh L, Kublickiene K. Endothelial function in conduit and resistance arteries in men with coronary disease. Atherosclerosis. 2006;184:130-6.
40. Kuvin J, Patel A, Kathleen A. Sliney K, Pandian N, Rand W, Udelson J, et al. Peripheral vascular endothelial function testing as a noninvasive indicator of coronary artery disease. J Am Coll Cardiol. 2001;38:1843–9.
41. Grover-Pa´ez F, Zavalza-Go´mez A. Endothelial dysfunction and cardiovascular risk factors. Diabetes Res Clin Pract. 2009;84:1-10.
42. Lekakis J, Papamichael C, Vemmos C, Voutsas A, Stamatelopoulos S, Moulopoulos S. Peripheral vascular endothelial dysfunction in patients with angina pectoris and normal coronary arteriograms. J Am Coll Cardiol. 1998;31:541-6.
43. Linke A, Schoene N, Gielen S, Hofer J, Sandra Erbs S, Schuler G, et al. Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. J Am Coll Cardiol. 2001;37:392–7.

44. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. Circulation. 2003;107:3152-8.
45. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001;38(3):860-6.
46. Vona M, Codeluppi G, Iannino T, Ferrari E, Bogousslavsky J, von Segesser L. Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction. Circulation. 2009;119:1601-8.
47. Edwards DG, Schofield RS, Lennon SL, Pierce GL, et al. Effect of exercise training on endothelial function in men with coronary artery disease. Am J Cardiol. 2004;93(5):617-20.
48. Moraca R, Lin E, Holmes Iv JH, Fordyce D, Campbell W, Ditkoff M, et al. Impaired baseline regional cerebral perfusion in patients referred for coronary artery bypass. J Thorac Cardiovasc Surg. 2006;131(3):540-6.
49. Anazodo UC, Shoemaker JK, Suskin N, Ssali T, Wang DJJ, St. Lawrence KS. Impaired cerebrovascular function in coronary artery disease patients and recovery following cardiac rehabilitation. Front Aging Neurosci. 2016;7(224).
50. Coombs GB, Al-Khazraji BK, Suskin N, Shoemaker JK. Impact of ischemic heart disease and cardiac rehabilitation on cerebrovascular compliance. J Appl Physiol (1985). 2023;135(4):753-62.
51. Anazodo UC, Shoemaker JK, Suskin N, St.Lawrence KS. An investigation of changes in regional gray mattter volume in cardiovascular disease patients, pre and post cardiovascular rehabilitation. Neuroimage Clin. 2013;3:388-95.
52. MacIntosh BJ, Swardfager W, Crane DE, Ranepura N, Saleem M, Oh PI, et al. Cardiopulmonary fitness correlates with regional cerebral grey matter perfusion and density in men with coronary artery disease. PLoS ONE. 2014;9(3):e91251.
53. Poirier SE, Suskin NG, Khaw AV, Thiessen JD, Shoemaker JK, Anazodo UC. Probing evidence of cerebral white matter microstructural disruptions in ischemic heart disease before and following cardiac rehabilitation: A diffusion tensor MR imaging study. J Magn Reson Imaging. 2023 (ePub ahead of print).
54. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLoS One. 2017;12(9):e0184244-e.
55. Griffo R, Ambrosetti M, Tramarin R, Fattirolli F, Temporelli PL, Vestri AR, et al. Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey. Int J Cardiol. 2012; 167(4):1390-5.
56. Guiraud T, Granger R, Bousquet V, Richard M, Soukarie L, Babin L, et al. Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program. Ann Phys Rehabil Med. 2012;55(5):312-21.
57. Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with heart disease--United States, 2005 and 2007. MMWR Morb Mortal Wkly Rep. 2009;58(7):165-9.
58. Rocha JA, Allison TG, Santoalha JM, Araujo V, Pereira FP, Maciel MJ. Muscoloskeletal complaints in cardiac rehabilitation: prevalence and impact on cardiovascular risk factor profile and functional and psychosocial status. Rev Port Cardiol. 2015;34(2):117-23.
59. Ong KL, Wu BJ, Cheung B, Barter PJ, Rye K-A. Arthritis: its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008. Ann Epidemiol. 2013;23:80-6.
60. Becker B. Aquatic therapy: Scientific foundations and clinical rehabilitation applications Am J Phys Med Rehabil. 2009;1(9):859-72.
61. The Editors of Encyclopedia Britannica. Archimedes' Principle. In: The Editors of Encyclopedia, editor. Encyclopedia Britannica: Encyclopedia Britannica, Inc.; 2020.
62. Orselli MIV, Duarte M. Joint forces and torques when walking in shallow water. J Biomech. 2011;44(6):1170-5.

63. Lee J, Lee R, Stone AJ. Combined aerobic and resistance training for peak oxygen uptake, muscle strength, and hypertrophy after coronary artery disease: A systematic review and meta-analysis. J Cardiovasc Transl Res. 2020;13(4):601-11.
64. Teffaha D, Mourot L, Vernochet P, Ounissi F, Regnard J, Monpere C, et al. Relevance of water gymnastics in rehabilitation programs in patients with chronic heart failure or coronary artery disease with normal left ventricular function. J Card Fail. 2011;17:676-83.
65. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Training-induced increase in nitric oxide metabolites in chronic heart failure and coronary artery disease: an extra benefit of water-based exercises? Eur J Cardiovasc Prev Rehabil. 2009;16:215-21.
66. Vasić D, Novaković M, Božič Mijovski M, Barbič Žagar B, Jug B. Short-term water- and land-based exercise training comparably improve exercise capacity and vascular function in patients after a recent coronary event: A pilot randomized controlled trial. Front Physiol. 2019;10(903).
67. Fiogbé E, Ferreira R, Sindorf MAG, Tavares SA, de Souza KP, de Castro Cesar M, et al. Water exercise in coronary artery disease patients, effects on heart rate variability, and body composition: A randomized controlled trial. Physiother Res Int. 2018;23(3):1-.
68. Volaklis K, Spassis A, Tomakadis S. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J. 2007;154:560.e1-.e6.
69. Tokmakidis SP, Spassis AT, Volaklis KA. Training, detraining and retraining effects after a water-based exercise program in patients with coronary artery disease. Cardiology. 2008;111(4):257-64.
70. Lee J-Y, Joo K-C, Brubaker PH. Aqua walking as an alternative exercise modality during cardiac rehabilitation for coronary artery disease in older patients with lower extremity osteoarthritis. BMC Cardiovasc Disord. 2017;17(1):252.
71. Gauer O. Recent advances in the physiology of whole body immersion. Acta Astronaut. 1975;2:31-9.
72. Ayme K, Gavarry O, Rossi P, Desruelle A-V, Regnard J, Boussuges A. Effect of head-out water immersion on vascular function in healthy subjects. Appl Physiol Nutr Metab. 2014;39(4):425-31.
73. Gabrielsen A, Warberg J, Christensen N, Bie P, Stadeager C, Pump B, et al. Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am J Physiol Regul Integr Comp Physiol. 2000;278:1583-8.
74. Park KS, Choi JK, Park YS. Cardiovascular regulation during water immersion. Appl Human Sci. 1999;18(6):233-41.
75. Christie J, Sheldahl L, Tristani F, Wann L, Sagar K, Levandoski S, et al. Cardiovascular regulation during head- out water immersion exercise. J Appl Physiol. 1990;69:657-64.
76. Boussuges A. Immersion in thermoneutral water: Effects on arterial compliance. Aviat Space Environ Med. 2006;77:1183-7.
77. Stadeager C, Johansen LB, Warberg J, Christensen NJ, Foldager N, Bie P, et al. Circulation, kidney function, and volume-regulating hormones during prolonged water immersion in humans. J Appl Physiol (1985). 1992;73(2):530.
78. Schmid J-P, Morger C, Noveanu M, Binder RK, Anderegg M, Saner H. Haemodynamic and arrhythmic effects of moderately cold (22°C) water immersion and swimming in patients with stable coronary artery disease and heart failure. Eur J Heart Fail. 2009;11(9):903-9.
79. Hanna RD, Sheldahl LM, Tristani FE. Effect of enhanced preload with head-out water immersion on exercise response in men with healed myocardial infarction. Am J Cardiol. 1993;71(12):1041-4.
80. Schmid JP, Noveanu M, Morger C, Gaillet R, Capoferri M, Anderegg M, et al. Influence of water immersion, water gymnastics and swimming on cardiac output in patients with heart failure. Heart. 2007;93(6):722-7.
81. Schega L, Claus G, Almeling M, Niklas A, Daly D. Cardiovascular responses during thermoneutral, head-out water immersion in patients with coronary artery disease. J Cardiopulm Rehabil. 2007;27:76-80.
82. Cider Å, Schaufelberger M, Andersson B, Sunnerhagen KS. Cardiorespiratory effects of warm water immersion in elderly patients with chronic heart failure. Clin Physiol Funct Imaging. 2005;25(6):313-7.
83. Pugh CJ, Sprung VS, Ono K, Spence AL, Thijssen DHJ, Carter HH, et al. The effect of water immersion during exercise on cerebral blood flow. Med Sci Sports Exerc. 2015;47(2):299-306.

84. Choi HJ, Kim RB, Joo JS, Han YE, Kim YS, Kim MS, et al. Comparison of cardiorespiratory responses during aquatic and land treadmill exercise in patients with coronary artery disease. J Cardiopulm Rehabil Prev. 2015;35(2):140-6.
85. Reilly T, Dowzer C, Cable N. The physiology of deep-water running. J Sports Sci. 2003;21:959-72.
86. Gabrielsen, VidebÆk, Johansen, Warberg, Christensen, Pump, et al. Forearm vascular and neuroendocrine responses to graded water immersion in humans. Acta Physiol Scand. 2000;169(2):87-94.
87. Carter HH, Cheng JL, MacDonald MJ, Pienaar O, Coleman A, Naylor LH, et al. The effects of exercise during water immersion on arterial function in humans. Am J Physiol Regul Integr Comp Physiol. 2023;324(4):R568-R73.
88. Tinken T, Thijssen D, Hopkins N, Dawson E, Cable T, Green D. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension. 2010;55:312-8.
89. Swift DL, Weltman JY, Patrie JT, Saliba SA, Gaesser GA, Barrett EJ, et al. Predictors of improvement in endothelial function after exercise training in a diverse sample of postmenopausal women. J Womens Health. 2014;23(3):260-6.
90. Suntraluck S, Tanaka H, Suksom D. The relative efficacy of land-based and water-based exercise training on macro- and microvascular functions in older patients with type 2 diabetes. J Aging Phys Act. 2017;25(3):446.
91. Nuttamonwarakul A, Amatyakul S, Suksom D. Effects of water-based versus land-based exercise training on cutaneous microvascular reactivity and C-reactive protein in older women with type 2 diabetes mellitus. J Exerc Physiol Online. 2014;17(4):27-33.
92. Carter HH, Spence AL, Pugh CJ, Ainslie P, Naylor LH, Green DJ. Cardiovascular responses to water immersion in humans: impact on cerebral perfusion. Am J Physiol Regul Integr Comp Physiol. 2014;306:R636-R40.
93. Sato D, Onishi H, Yamashiro K, Iwabe T, Shimoyama Y, Maruyama A. Water immersion to the femur level affects cerebral cortical activity in humans: Functional near-infrared spectroscopy study. Brain Topogr. 2012;25(2):220-7.
94. Green D, Kurt. S, Maslen B, Cox K, Lautenshlager N, Pestell C, et al. The impact of six-month land versus water walking on cerebrovascular function in the aging brain. Med Sci Sports Exerc. 2021 53(10):2093-100.
95. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559.
96. Alsaleh E, Baniyasin F. Prevalence of physical activity levels and perceived benefits of and barriers to physical activity among Jordanian patients with coronary heart disease: A cross-sectional study. Front Public Health. 2022;10:1041428.
97. Huang W-T, Liu C-Y, Hung H-F, Hsu S-P, Chiou A-F. Gender differences in factors associated with physical activity in patients with coronary artery disease. J Cardiovasc Nurs. 2022;37(4):386-77.
98. Reid RD, Morrin LI, Pipe AL, Dafoe WA, Higginson LAJ, Wielgosz AT, et al. Determinants of physical activity after hospitalization for coronary artery disease: the Tracking Exercise After Cardiac Hospitalization (TEACH) Study. Eur J Cardiovasc Prev Rehabil. 2006;13(4):529-37.
99. Evenson KR, Butler EN, Rosamond WD. Prevalence of physical activity and sedentary behavior among adults with cardiovascular disease in the United States. J Cardiopulm Rehabil Prev. 2014;34(6):406-19.
100. Driscoll A, Hinde S, Harrison A, Bojke L, Doherty P. Estimating the health loss due to poor engagement with cardiac rehabilitation in Australia. Int J Cardiol. 2020;317:7-12.

Chapter 2. Literature review

2.1 Coronary heart disease

Coronary heart disease (CHD) is a chronic, non-communicable sub-type of cardiovascular disease (CVD) that affects perfusion of the myocardium due to a narrowing or blockage of the coronary vessels (1). Other common terms for CHD include coronary artery disease and ischaemic heart disease. The pathophysiology of CHD is commonly associated with dysfunction of the endothelium, leading to the development of atherosclerosis (1). There are non-modifiable characteristics, such as age and sex, and a range of behavioural, biomedical, and psychosocial risk factors that predispose an individual to developing CHD (2). Furthermore, CHD is associated with several other chronic health conditions, such as arthritis, diabetes and heart failure (3). There is a significant fatal, non-fatal and financial burden associated with CHD, including being the leading cause of death globally in 2019 (4). In Australia, the direct heath expenditure associated with CHD was estimated at $2.4 billion in 2018-2019 (5).

2.1.1 Aetiology and pathophysiology

Coronary heart disease occurs when atherosclerotic lesions develop in the coronary arteries (1). These lesions can reduce the blood supply to the myocardium causing angina, and if a lesion ruptures the resulting thrombus can completely occlude the artery resulting in a myocardial infarction (MI) (6). While CHD is a chronic condition, acute episodes can occur known as acute coronary syndromes (ACS). The most severe type of ACS is a ST segment elevated myocardial infarction (STEMI), where there is elevation of the ST segment of an electrocardiogram (ECG), and this is typically caused by a complete obstruction of a coronary artery leading to cell necrosis (7). The next category is a non-ST segment elevation myocardial infarction (NSTEMI), where there is no elevation of the ST segment on ECG, and it is usually caused by a partially blocked artery severely restricting blood flow (7). The final category of ACS is unstable angina, where there is a change in the severity of partial coronary artery blockages, and this can progress to NSTEMI or STEMI (7). While not categorised as an ACS, acute symptoms of angina can occur when there is a temporary period when myocardial oxygen demand is not met by supply, such as during physical or emotional stress (7).

2.1.1.1 Vascular structure and function

The structure of the arterial wall is shown in Figure 2.1.and consists of three layers, the tunica intima, tunica media and tunica externa (or adventitia) (8). While the three layers occur throughout the arterial tree, the composition varies based on the location of the artery. For example, the aorta, an elastic artery, has a greater content of elastin per surface area than the femoral artery, a muscular/conduit artery (9). The tunica intima separates the lumen from the rest of the vessel wall (8) and consists of a single layer of endothelial cells, referred to as the endothelium, and the basement membrane consisting of collagen and glycoproteins, with the elastic fibres of the elastica interna forming the interface with the tunica media (10). The tunica media consists of vascular smooth muscle cells, along with collagen and elastic tissue (8). The elastica externa forms the boundary between the tunica media and the tunica externa (also termed tunica adventitia), which is predominantly composed of connective tissue (8).

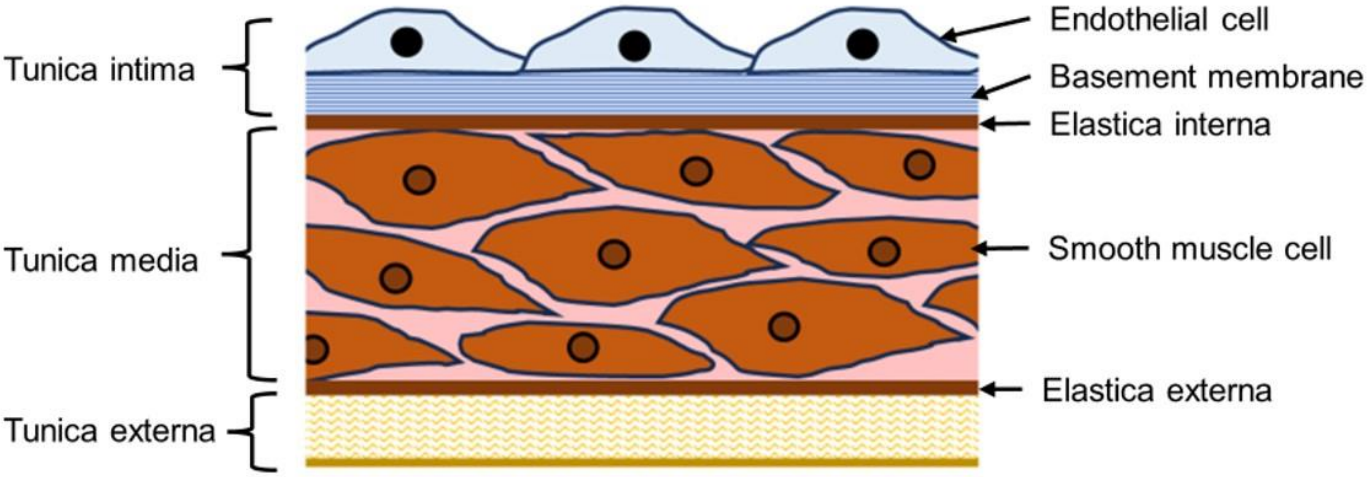


Figure 2.1 Arterial wall structure

The endothelium releases signalling molecules in response to changes in chemicals in the blood and changes in blood flow or pressure (8). These vasoactive signalling molecules can lead to vasodilation or vasoconstriction though acting on the smooth muscle in the tunica media layer (11). One of the potent stimuli for vasodilation is wall shear stress, which describes the friction of blood on the endothelium (12). The wall shear stress can be calculated through Equation 1 (12).

Equation 1 Wall shear stress:

$$Wall\ shear\ stress = \frac{blood\ viscosity\ x\ blood\ flow\ velocity}{arterial\ diameter}$$

Increased wall shear stress on endothelial cells in vitro has been shown to lead to the production of nitric oxide (NO) (13) and prostaglandins (14). During in vivo studies, NO was determined to play a role in the vasodilation response to increased blood flow (15), with endothelial nitric oxide synthase (eNOS) the implicated biological catalyst to endogenous NO production (11, 16). Additionally, when released into the blood, NO can reduce platelet (17) and leukocyte (18) adhesion. Other roles of the endothelium include regulating vascular smooth muscle cell proliferation and mitogenesis (19).

Endothelial function can be assessed using a range of invasive and non-invasive techniques (20). In-vivo techniques used to measure endothelial function can include: intra-arterial or intra-venous infusions to induce arterial diameter changes (e.g. intra-brachial infusion of acetylcholine), flow mediated dilation ([FMD] which utilises ultrasound to assess post-occlusion reactive hyperaemia in conduit vessels), peripheral arterial tonometry / reactive hyperaemia index (which assesses microvascular function using post-occlusion reactive hyperaemia), and laser Doppler imaging for skin microvascular function (which assesses changes in flow in response to a range of potential stimuli, such as cuff occlusion or heating) (20). Venous occlusion plethysmography has also been utilised, which assesses changes in limb volume with a sub-diastolic pressure cuff inflation (20).

2.1.1.2 Endothelial dysfunction and atherosclerosis

Dysfunction in the endothelium increases the risk of atherosclerosis developing through allowing lipids and fibrous elements to accumulate within the vessel wall (1). Certain stimuli can predispose the endothelium to becoming dysfunctional, such as hypertension, which alters shear stress patterns leading to increases in reactive oxygen species and inflammation (21). Other states that challenge the endothelium include elevated lipid levels, products of glycoxidation (from hyperglycaemia) and the release of pro-inflammatory cytokines (22).

These challenging states can lead to an increased expression of adhesion molecules in the endothelial cells (22), which in turn increases leukocyte adhesion (18) and migration into the intima (22), promoting the development of atherosclerotic plaque. The most common sites for lesions are in areas of low shear stress and turbulent or oscillatory blood flow, such as very curved vessel regions, or surrounding artery branch points, where

there are regions of endothelium where there is increased contact time between particles in the blood and the endothelial cells (23).

Pre-clinical lesions start with a ‘fatty streak’ of macrophages engorged with lipids that have migrated into the intima (1). Once in the intima and in the presence of inflammatory molecules, the leukocytes (predominantly T lymphocytes and macrophages) can communicate with the smooth muscle cells of the media and these cells can migrate into the intima and proliferate, producing an extracellular matrix (22). Substances in the extracellular matrix, mainly proteoglycans, can bind with lipids, not only keeping them in the intima, but also increasing their susceptibility to glycation. Glycation end products, such as oxidised phospholipids, can further sustain and propagate the inflammatory response (22). Lesions can calcify during progression and soft lipid ‘necrotic’ cores can develop due to death of the lipid rich leukocytes trapped in the intima (1, 22). During the earlier stages of the atherosclerotic process, lesions extend extraluminally (22) and the vessel remodels outwards around this, to a limit, prior to encroaching on the lumen (24). By the time a plaque forms a stenosis, there is often an extensive distribution of atherosclerotic lesions (22). Improvements in plaque imaging have found that lesions with high plaque burden, thin fibro-atheroma caps, low attenuation, and outward remodelling are more vulnerable to progress, and plaque progression is linked to a substantially higher risk of further coronary events (24). If an atherosclerotic lesion ruptures, a thrombus (blood clot) can form, which can result in MI or stroke, depending on the location (1). If the lesion is untreated and occludes the vessel, end-organ damage can occur to the area supplied by the vessel (25), such as the myocardium if this occurs in the vessels supplying the heart (22).

The systemic nature of the atherosclerotic process was highlighted by a study, which investigated atherosclerotic burden in 4,184 asymptomatic adults aged between 40-54 years of age (26). Accenting the ‘silent’ nature of the early stages of disease, 71% of males and 48% of females demonstrated subclinical atherosclerosis, with 41% of participants displaying disease across multiple assessment sites (26). Furthermore, subclinical atherosclerosis was present in nearly 60% of people classified as having a low 10 year risk of CHD using the Framingham Heart Study criteria (26).

Given the diffuse nature of atherosclerosis, even in apparently healthy individuals, adherence to secondary prevention strategies is especially important in those with clinical disease, as there are likely numerous smaller lesions to manage to prevent further clinical issues. As the endothelium is the ‘gate keeper’ to this atherosclerotic process, it is a logical target for interventions to reduce CHD burden.

2.1.2 Prevalence, trends and demographics of coronary heart disease

Coronary heart disease is a prevalent global health issue. It was estimated that 244 million people were affected by CHD in 2020 (27), with over half a million people affected in Australia in 2020-2021 (5). Globally, CHD prevalence has increased since 1990 (27, 28), although there is a wide disparity in CHD trends between countries (28). While the rate of acute coronary events has declined in Australia (5), the populations structure is ageing (29), indicating a significant future problem. Demographically, males are more likely to be affected (27), along with older individuals (28, 30, 31), First Nations people (32), people from lower socioeconomic backgrounds (27, 33) and particular geographic regions such as Eastern Europe, North Africa and the Middle East (27, 28).

The estimated global prevalence of CHD in 2020 was 244.1 million people (95% CI 213.5-275.8 million people), with an age-standardised rate of 2,919.8 per 100,000 (95% CI 2555.3 to 3296.6 per 100,000 people) (27). Estimation of true CHD prevalence is challenging due to differences in, and issues with, reporting between countries (34). Australian data estimated the national prevalence of CHD ranged between 2.9-3.1% of the population over the past 5 years (~571,000 to 580,000 people) (5). The global incidence of CHD was estimated to be 21.2 million people (95% CI 18.9-23.7 million people) in 2019 (35). In Australia 56,700 acute coronary events (MI or unstable angina) occurred in 2020 (5) which is used as a surrogate marker for the incidence for CHD in Australia (36). These figures highlight CHD as a significant global and Australian health problem.

There have been disparate trends in prevalence and incidence of CHD across the world. Globally, there was a 34.9% (95%CI 31.3-38.4%) increase in the prevalence of CHD between 2010 and 2020, despite a relatively small increase in the age-standardised rate (1.80%, 95% CI -0.72 to 4.3%) (27). Contrastingly, the prevalence of CHD in Australia has been relatively stable since 2011, around 3% (5, 36), despite age standardised (5) and overall (37) rates of acute coronary events having fallen in Australia over the past 20 years. The age structure of the population may be a contributing factor to this, as CHD prevalence increases with age, particularly from 55 years onward (32), with the prevalence in people aged between 75 years and over 14%, compared to 1% in people aged 45 to 54 years (5). In Australia, the proportion of the population aged 65 years and over, who are at an elevated risk of CHD (37), has increased from 11% to 17% over the past 30 years (29). This proportional increase is expected to continue over the next 30 years, with those aged 65 years and over anticipated to increase to 22% of the Australian population in 2053 (based

on analysis by the Centre for Population) (38). Given the association found between CHD prevalence and age (39), this ageing population structure is likely to impact the number of people living with CHD into the future.

Demographically, global data indicate that males are more likely to be diagnosed with CHD than females, with 141.0 million (95% CI 123.6 to 159.2 million) males having CHD, compared to 103.1 million (95% CI 89.4 to 117.4 million) females (27). This observation is reflected in Australian data, after age adjustment, with 3.8% of males and 1.9% of females reported as having CHD in 2017-2018 (37). Of note, global age standardised rates have been increasing in females (by 2.09%, 95% CI 0.32-3.89% from 1990-2020 and by 3.30%, 95% CI 0.72-6.22% between 2010 and 2020), whilst global age standardised rates decreased in males from 1990 to 2020 (-2.27% , 95% CI -3.51 to -1.00), and stabilised between 2010-2020 (27).

First Nations Australians were found to have a prevalence of CHD 2.8 times greater than non-Indigenous Australians in 2017-2018 (5), with a higher prevalence of CHD reported in First Nations people around the world (40, 41). American Indian or Native Alaskan peoples had 1.5 times the prevalence of Caucasian people in the United States (40), and Māori people had 1.5-2.4 times the prevalence of CHD as people of European descent in New Zealand (41), all highlighting the profound impact of CHD on First Nations peoples. Additionally, First Nations Australians were found to be affected at a younger age than non-indigenous Australians (42).

Socioeconomic status has been reported to impact CHD prevalence. In Australia, the population group with the lowest socioeconomic status had a CHD prevalence 1.6 times that of the group with the highest socioeconomic status (5), with a similar disparity (1.7 times) in the United States (40). Furthermore, Australians from the lowest socioeconomic areas are 1.5-1.75 times more likely to have a MI than those from the highest socioeconomic areas (33).

In 2020, the regions with the highest age-standardised prevalence of CHD were Eastern Europe, North Africa, the Middle East, and Central and South Asia (27), with Eastern Europe found to have particularly high prevalence. For example, Russia was found to have an estimated prevalence of 4,198 per 100,000 people, compared to an estimated prevalence of 704 per 100,000 people in South Korea (28). It has been acknowledged that in low and middle income countries there is earlier disease onset compared to high income countries (43). Disparities between nations may be due to differences in the recording of

CHD cases, risk factors, treatments and primary and secondary prevention strategies (34). While the overall prevalence of CHD in Australia is lower than many other nations (28), within Australia, remote and very remote residents had age-standardised CHD hospitalisation rates of 745 per 100,000 people, which was 1.5 times the rate of those living in major cities (486 per 100,000 people) in 2020-2021 (5).

These statistics highlight the need for improved primary prevention strategies for CHD. Additionally, the current disparities in CHD prevalence with socioeconomic status and for First Nations peoples, emphasise that further measures are needed to improve cardiac health in the most vulnerable populations. The high number of people living with CHD globally, and the projected ageing of the Australian population, highlight the need for diverse and effective secondary prevention strategies to manage this chronic condition into the future.

2.1.3 Burden of disease

Coronary heart disease is the leading cause of disease burden in Australia and has been since this was first assessed as an outcome in Australia in 2003 (44). Disease burden represents both fatal and non-fatal (living in ill-health) components (44). The total burden of CHD in Australia has reduced over time, due to a reduction in fatal burden, but CHD remains the leading specific cause of disease burden, and represented 5.5% of the overall disease burden in Australia in 2022 (44). Despite improvements in survival in people with CHD, it remained the global leading cause of death in 2019 (4). Furthermore, there are substantial non-fatal and financial implications of the disease, through living with a chronic condition, the direct medical costs and indirect costs to individuals living with the condition and the economy.

2.1.3.1 Mortality

Coronary heart disease is the leading cause of death both globally and in Australia (4, 45). In 2019, approximately 8.9 million deaths occurred due to CHD globally, equating to 16% of global deaths and continuing the trend of CHD being the leading cause of death over the past 20 years (4). This is an increase since 2000, when 6.7 million deaths from CHD (13% of global deaths) were reported (4). In Australia, while the fatal burden of CHD has reduced since the late 1960s, CHD was still the leading cause of death in 2022, causing approximately 20,000 deaths, corresponding to 9.8% of total deaths (45).

Survival from coronary events in Australia has improved dramatically over the last 40 years (46), with a 38% decline in total CHD deaths since 1985 and declines in the CHD mortality rate from 377 to 89 per 100,000 in males, and from 201 to 48 per 100,000 in females (32). Data from across Australia and New Zealand from 239,402 initial MI admissions found that while short term (6 month) survival was better in those who had a NSTEMI, the 7-year survival rate was higher after STEMI (70.8%) than NSTEMI (62.3%), with an 85% survival rate for those aged under 65 years old at the index admission (47). Those who underwent revascularisation (72% of STEMI, 42% of NSTEMI patients) had an 80% survival rate, compared to 45% in those who did not receive revascularisation (47). The improved initial and subsequent survival in Australia has been attributed to improvements in early detection and treatment. While these reductions in mortality are encouraging, the population structure in Australia is ageing (38) and there is a high burden of risk factors and multimorbidity (5), which will likely lead to CHD remaining a leading cause of mortality into the future.

2.1.3.2 Non-fatal burden

The non-fatal burden from CHD has also decreased over time in Australia (44) with more variation found in global statistics (48). Epidemiologically, non-fatal burden is often termed ‘years lived with disability’ (YLD) (44). The 2017 Global Burden of Disease Study estimated that 126.5 million people were living with CHD, causing 5.3 million (95% uncertainty interval 3.7-7.2 million) YLD (48). In Australia, in 2022, the estimated YLD for CHD was 68,452 (44). Between 2003 and 2022 the age-standardised rates for YLD dropped in both sexes (from 5.05 to 2.66 per 1,000 of population in males, and from 2.66 to 1.33 per 1,000 of population in females) (44). While on a population scale this is a positive development, on an individual level quality of life is still profoundly impacted in people with CHD. A longitudinal study of 9,566 MI survivors (25% female, mean age 64 years) found that 69% reported one or more perceived other health problems during their index admission (49). Despite an average improvement in perceived health problems, these problems persisted in 60% of participants at 12 months follow up (49). Females, those with comorbidities, and NSTEMI survivors had poorer quality of life outcomes at 12 months (49). These studies highlight that while on a population scale there has been improvement in the non-fatal burden of CHD, at an individual level there is often an adverse impact on daily life and functioning, highlighting the need for further refinement of rehabilitation treatments.

2.1.3.3 Financial

Coronary heart disease places a substantial financial burden both on the economy and individuals, with direct healthcare costs (27, 50). and loss of productivity (27, 51). Additionally, households living with people with CHD may face financial strain (52). In the United States, the estimated healthcare costs of heart disease, including CHD, was $108.8 billion dollars in 2017-2018, the 6th leading cause of health expenditure, while the indirect costs from lost productivity or mortality were $119.9 billion (27). In Australia, in 2018-2019, an estimated $2.35 billion was spent on direct costs of treating CHD (50). The key expenses from these data were $823 million on public hospital admissions, $892 million on private hospital services, $104 million on public hospital emergency department visits, $156 million for pharmaceutical benefits scheme medications, $101 million for specialist services and $72 million for general practitioner visits (50), highlighting the significant direct healthcare costs to the economy.

2.1.3.4 Summary

Coronary heart disease places a profound burden on society. While mortality has improved over time, it is still the leading cause of death globally and in Australia. Additionally, there is a significant non-fatal burden due to the chronicity of the disease, both in terms of YLD and quality of life changes. Financially, the cost of managing CHD causes strain due to productivity loss and medical expenses to the broader economy. While incidence rates of CHD may be reducing in Australia, the changes in population structure have led to a growing number of people living with CHD as a chronic condition, highlighting the need for strategies to reduce the burden of this disease on individuals and the economy into the future.

2.1.4 Risk factors for coronary heart disease

The Framingham Heart Study first coined the term ‘risk factor’ in the early 1960s, and today risk factor is defined as an attribute, exposure or characteristic associated with an increased probability of a person developing a health condition (5). Cardiovascular disease risk factors can be classed as demographic/non-modifiable, behavioural, biomedical and psychosocial (2) (see Figure 2.2). It has been recognised that there can be a cumulative impact of risk factors in CVD development (53).

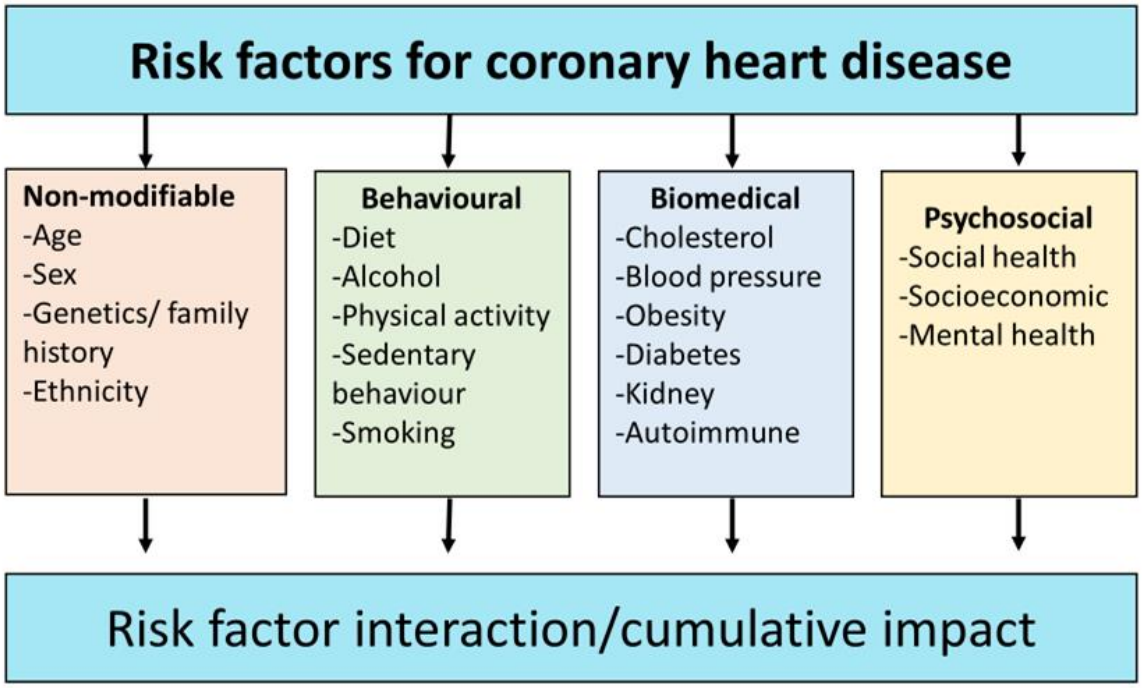


Figure 2.2 Risk factors for cardiovascular disease.

2.1.4.1 Non-modifiable risk factors

Non-modifiable risk factors include demographic factors (such as age, sex and ethnicity) and other characteristics (such as family history or genetics) that predispose an individual to CHD development. These factors cannot be changed through lifestyle modifications or medications.

Adults over the age of 55 years are more likely to develop CHD (32), with details of the demographics outlined in Section 2.1.2. Absolute 5 year risk scores found ‘high’ ratings for CVD risk for 2.1% of those aged 35 to 44 years, up to 37.3% in those aged 75 years and older (54). For developed nations such as Australia this is likely to pose a significant problem in the future, with the projected proportional increase in people aged 65 years and over in the next 20 years (38).

In Australia, the age standardised prevalence of CHD in 2017-2018 CHD was higher in males (3.8%) than females (1.9%) (55) and this was reflected in global data (27). There are some female-specific risk factors for CHD development, including early menarche (56), early menopause (57, 58) and polycystic ovarian syndrome (56). Furthermore, pregnancy complications, including hypertensive and metabolic disorders of pregnancy, have been associated with a substantial increase in the risk of CHD development in later life for females (57, 59, 60).

Genetics appear to play a role in CHD development, with a study of twins finding moderate heritability for males and females, more so for premature disease onset (61). Further studies have demonstrated that a history of CVD in parents or first-degree relatives is associated with an increased risk to individuals, with premature CVD onset in relatives associated with higher risk (62-64). Genetic studies have identified many potential targets for CHD, with over 200 loci associated with CHD, rather than one primary genetic determinant (65). Allele differences in the interlukin-6-receptor pathway, which is linked to inflammation, have been found to lower the risk of CVD (66). Work is ongoing in this area, with population specific markers being identified (67).

Higher rates of CHD have been seen in African-American and First Nations Australian populations, compared to non-indigenous/Caucasian populations (5, 68), and in Han Chinese compared to ethnic minorities (69). Additionally, higher CHD related deaths have been observed in South Asian migrants to America, compared to non-Hispanic people of European descent (70). In New Zealand, Pacific Islander, Māori and Indian people had a higher risk of CVD than people of European descent, whilst those of Chinese or other Asian descent were at a lower risk compared to those of European descent (71). Some of the disparities between different ethnic groups may be related to differences in risk factor profiles (53, 68, 72, 73).

The non-modifiable risk factors for CHD highlight the increasing risks with older age, male sex, female sex-specific conditions, early onset of CHD in a family history, and an Indigenous or minority ethnicity or cultural background. These characteristics highlight the need to cater to a wide range of people within cardiac rehabilitation (CR) and exercise program designs, particularly ensuring the included exercises are suitable for older adults.

2.1.4.2 Behavioural risk factors

Behavioural risk factors have also been referred to as ‘lifestyle’ risk factors historically, and these are the target of secondary prevention programs. These factors include diet and alcohol intake, physical inactivity and smoking (2).

2.1.4.2.1 Diet and alcohol

Diet and high alcohol use have been identified as behaviour-related risk factors for CHD development (74-76). Poor diet was the second highest scoring risk factor in CHD and CVD in the Global Burden of Disease Study, with 6.9 million deaths attributed to diet-related CVD (74). The key dietary change related to the CVD death and disability rates varied between

geographic regions. A meta-analysis of diet related studies (22 studies, 70,273 participants) found that a high intake of nuts, fruit, vegetables and whole grains substantially reduced the risk of cardiovascular death, while red or processed meat increased the risk (77). A 2015 study in Australia attributed 40.2% of the risk of CVD to dietary risks (78), highlighting the importance of this risk factor and the inclusion of dietary support within CR programs.

The impact of alcohol consumption on cardiovascular risk has been varied in the literature, with some studies finding a small cardioprotective effect of low-level alcohol intake (58), while other studies have suggested this effect is due to confounding lifestyle factors (75, 76). After adjustment for lifestyle factors, the 'protective' effect of low-level alcohol intake has been shown to be reduced in large (370,000-600,000 people) cohort studies (75, 76).

2.1.4.2.2 Physical activity and sedentary behaviour

The World Health Organisation acknowledges insufficient physical activity as a leading risk factor for non-communicable disease burden, with projections of new non-communicable disease presentations due to physical inactivity approaching 500 million cases between 2020-2030, at an estimated cost of $USD300 billion (79). Compared to people who perform 30 minutes per day of moderate intensity physical activity, people who are inactive have a 20-30% higher risk of all-cause mortality (80). In Australia 8% of the burden of CVD and 11% of the burden of CHD has been attributed to insufficient physical activity (81) (82).

The impact of physical activity on MI risk has been examined in a broad reaching global study. Yusuf et al. (2004) conducted a case control study across 52 countries and determined that physical activity (≥4 hours of moderate or vigorous physical activity, or exercise, per week) reduced the risk of MI compared to no regular physical activity, when adjusting for other risk factors (OR 0.86, 99% CI 0.76-0.97) (83). Furthermore, physical inactivity was associated with 12% of the population attributable risk for MI (83). The benefit of physical activity and exercise varied across populations, with greater population attributable risk attributed to low physical activity in females (females: 27.1%, males: 9.3%) and certain geographic regions (23.8% for Australia and New Zealand, 38.4% for Western Europe, 4.2% for Middle East) (83).

The Australian Physical Activity Guidelines from the Australian Government Department of Health encourage people who are inactive to become active, which may

mean beginning below the current recommendations and gradually building up. The current recommendations are:

- Be active on as many days of the week as possible
- Aerobic: accumulate 150-300 minutes (600-1200 MET/minutes) of moderate intensity physical activity, or 75-150 minutes (1600-1200 MET/minutes) of vigorous intensity physical activity, or an equivalent combination of both, weekly
- Perform muscle strengthening exercise at least twice per week (84).

In Australia, adherence to meeting all aspects of the guidelines is low (17.3% in 2017-2018 (73), 28% in 2020-2021 (85)). In 2017-2018, 61% of adults reported doing at least 150 minutes per week of any level of physical activity, with 15% reporting no physical activity at all (73). Meanwhile, exercise participation of at least 150 minutes/week was met by 55% of those aged 18-64 years and 42% of those aged 65 years and older in 2017-2018 (73).

International data demonstrate varied findings on physical activity levels. A pooled analysis of data, from 168 countries and 1.9 million participants in 2016, found the global age-standardised prevalence of physical inactivity was 27.5% (95% uncertainty interval 25.0-32.2%) (86). Rates varied widely between regions, ranging from 43.7% (95% uncertainty interval 42.9-46.5%) in Latin America and the Caribbean, to 17.6% (95% uncertainty interval 15.7-23.9%) in east and southeast Asia (86). In the United States, 24.2% of people aged over 18 met the American 2018 Physical Activity Guidelines in full in 2020, with 31% meeting muscle strengthening guidelines, 46.9% meeting aerobic exercise guidelines and 46.3% meeting neither guideline (87). Globally, females had higher levels of insufficient physical activity than males (31.7% vs 23.4%) (86). These studies suggest that there is a substantial risk from insufficient physical activity for CVD and CHD development, and that there is a large portion of people who are not meeting physical activity guidelines.

Sedentary behaviour

Further to a lack of physical activity, sedentary behaviour (activity of up to 1.5 METS , in a supported posture, such as lying down or sitting (88)) has been found through a meta-analysis to independently increase the risk of all-cause mortality in all but the most active individuals (those who perform at least 60-75min of moderate intensity exercise per day) (89) and to increase the risk of CVD morbidity and mortality (90). In Australian adults, increased time spent in sitting increased all-cause mortality, even after adjusting for physical

activity levels, with risks significantly increasing for those sitting more than 8 hours per day (91). Accordingly, the Australian guidelines now include advice to reduce sedentary behaviour, encouraging people to avoid, or break up periods of prolonged sitting as often as possible (84). The prevalence of prolonged sedentary behaviour is high. In Australia, Van der Ploeg et al. (2012) found 25% of Australian adults surveyed reported sitting at least 8 hours per day. Internationally, approximately 37% of adult respondents in Singapore reported sitting 8 or more hours per day (92), whilst an American study, using a 24 hour recall approach, found the average sitting time was 9.5 hours per day, with 50% of respondents reporting sitting for more than 9.5 hours per day (93). These studies show a high number of adults engage in sedentary behaviour at a level known to increase risk of mortality and CVD.

2.1.4.2.3 Smoking

Tobacco smoking has been associated with an increased risk of CVD development for both males and females and is an important component of risk calculations (58). In Australia, an estimated 13.8% of the Australian population were daily smokers in 2017-2018 (73), and smoking was linked to a substantial disease burden, with 11.5% of the burden of CVD attributed to tobacco use (78). Furthermore, in those aged under 65 years, one quarter of ACS hospitalisations and one third of CVD deaths could be attributed to smoking (94). The adjusted relative risk of CHD development was 1.16 and 1.65 times higher in former, and current smokers, compared to those who never smoked (94). International data supports this association, with an additional finding of earlier onset of CHD by approximately 10 years in people who smoke (95). Approximately 72% of people with CHD who were aged under 45 years were current smokers, compared to approximately 30% of males and 42% of females with CHD in the overall meta-analysis sample (95). These data suggest smoking is associated with an increased risk of CHD development at an earlier age and is accordingly attributed a high degree of disease burden.

2.1.4.3 Biomedical risk factors

Biomedical risk factors for CHD are bodily states which increase the probability of developing CHD (96). Biomedical risk factors for CHD are shared with other types of CVD and several are associated with other chronic conditions, such as diabetes and chronic kidney disease (96). The key biomedical risk factors for CHD are elevated blood pressure, adverse lipid profiles, obesity and diabetes. Additionally, there are female-specific risk

factors (including early menopause or menarche, and hypertensive or metabolic disorders of pregnancy), which were covered in Section 2.1.4.1.

2.1.4.3.1 Blood pressure and hypertension

One of the initial risk factors for CHD discovered by the Framingham Heart Study was hypertension (97). The current High Blood Pressure Clinical Practice Guidelines define stage 1 hypertension as systolic blood pressure (SBP) between 130 and 139mmHg, or diastolic blood pressure (DBP) between 80-89mmHg, and stage 2 hypertension as SBP ≥140mmHg or DBP ≥90mmHg (98), although many risk factor and prevalence studies have used the current stage 2 definition as the definition of hypertension (5, 99).

A large international case-control study of people hospitalised with an initial MI (n=15,512 cases, n=14820 controls, 52 countries) found self-reported hypertension was associated with an adjusted odds ratio of 1.91 (99% CI 1.74-2.10) for acute MI, compared to people without self-reported hypertension (83). Furthermore, the overall population attributable risk for MI associated with hypertension was 17.9% (99% CI 15.7-20.4) (83). Other studies have reported an association between hypertension and the development of CHD or CVD (5, 99, 100). In 2017-2018 approximately 34% of Australian adults had hypertension (defined per stage 2 hypertension above), with two-thirds of these cases not being adequately controlled by medication (5). Hypertension was estimated to contribute approximately 38% of the burden of CVD in Australia in 2015 (78). Given the large numbers of people with uncontrolled hypertension, the large burden of disease attributed to this risk factor, and the strong link to CHD, this risk factor is significant for preventive strategies.

2.1.4.3.2 Lipid profiles

Along with hypertension, the lipid profile was one of the earliest targets identified by the Framingham Heart Study (97). Elevated measures of total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglycerides have been associated with CHD development (97, 101, 102), while higher levels of high density lipoprotein cholesterol (HDL-C) have been associated with a protective effect (97), except with extreme elevation (103).

While a meta-analysis of over 1 million participants found elevated total cholesterol was associated with increased risk of CHD development (104), this risk appears to be reversible with management, as a reduction in elevated levels is associated with an adjusted hazard ratio of 0.73 (95% CI 0.58-0.91) for cardiovascular events, compared to people with persistently elevated cholesterol (99). When investigated as components of the lipid profile,

increased LDL-C has been associated with greater risk of CHD (101) and MI (102), and triglycerides have been associated with an overall increased risk of CHD, even when LDL-C levels are normal (101). Non-HDL-C (total cholesterol minus HDL-C) has been identified as another potential predictor for CHD development (101). In patients with low LDL-C (<100mg/dL) this marker may be particularly useful for discerning future CHD development, as the hazard ratio increases to 1.84 (95% CI 1.12-3.04) when non-HDL is ≥130mg/dL (compared to <130mg/dL) (101). While HDL-C has historically been considered to be protective for CHD development and raising HDL levels has become a therapeutic target (97), contemporary data suggests this association may be 'U' shaped, with extremely high HDL-C levels also associated with increased all-cause mortality (103).

In Australia in 2011-2012, 63% of adults exhibited dyslipidaemia (at least one of the following: total cholesterol ≥5.0mmol.L^{-1}, LDL cholesterol ≥3.5mmol.L^{-1}, HDL <1.0mmol.L^{-1} in males or <1.3mmmol.L^{-1} in females, triglycerides ≥2.0mmol.L^{-1}, on any lipid modifying medications) (105). These studies demonstrate that dyslipidaemia is common, and the whole lipid profile should be examined in determining a person's CHD risk, with improvements in lipid profile over time associated with reduced CHD risk.

2.1.4.3.3 Overweight and obesity

Classifications of overweight and obesity are often done by calculating body mass index (BMI), with categories including underweight (BMI <18.5kg.m^2), normal weight (BMI 18.5-24.9kg.m^2), overweight (BMI 25.0-29.9kg.m^2) and obese (BMI ≥30kg.m^2) (106). Being overweight or obese increases the risk of CHD development (107), with the age-adjusted relative risk for CVD for overweight females being 1.20 (95% CI 1.03-1.40) and for males was 1.21 (95% CI 1.05-1.40), increasing to 1.64 (95% CI 1.37-1.98) in obese females and 1.46 (95% CI 1.20-1.77) in obese males, when compared to normal weight individuals (106). The population attributable risk of being overweight (BMI of at least 25kg.m^2) was 23% for males and 15% for females for CHD (106). A review by Katta et al. (2021) found that most studies agreed being overweight or obese, particularly centrally obese, increased the risk of CHD development (107). Measures of central adiposity, such as waist circumference, may provide more detail than weight or BMI on CHD risk (107). Approximately 67% of Australian adults are overweight or obese (5) and in keeping with the international data, 19.3% of the burden of CVD has been attributed to this (78). Given the substantial proportion of the population who are in the 'at risk' category, overweight and obesity is an important issue to address in primary prevention of CVD.

2.1.4.3.4 Diabetes mellitus

Type 1 and type 2 diabetes mellitus have been acknowledged as a risk factors for CHD development (108, 109), as has a history of gestational diabetes mellitus (110). Type 1 diabetes is an autoimmune condition where the pancreas does not produce sufficient insulin, while in type 2 diabetes there is a gradual increase in insulin resistance in the body, combined with a gradual reduction in the capacity for the pancreas to produce insulin (111). Gestational diabetes is a glucose intolerance that first develops during pregnancy, which may resolve after pregnancy (111).

An international case-control study of 15,152 cases and 14,820 control participants found the adjusted odds ratio for MI in people with any diabetes mellitus was 2.37 (99% CI 2.07-2.71) and the overall population attributable risk for MI was 9.9% (99% CI 8.5-11.5%) (83). Increased risk of incident CHD or cardiovascular events have been observed in people with type 1 (108, 112) and type 2 diabetes (109), and a history of gestational diabetes was found to increase the risk of incident CHD, MI and angina (110).

In Australia, 4.9% of the population had diabetes in 2017-2018 and based on self-reported data, 57% of people with diabetes had comorbid CVD (5). In 2020-2021, 17.9% of females who gave birth had gestational diabetes (111). Approximately 5% of the burden of CVD in Australia has been attributed to high plasma glucose (78). These studies highlight the imperative for closely monitoring cardiovascular risk factors in patients with diabetes.

Given the increased risk of CHD in people with diabetes and the high prevalence of diabetes in people with CHD (95), some considerations for people with diabetes should be considered when designing exercise programs for people with CHD. These would include monitoring for potential hypoglycaemia, ensuring adequate foot protection, particularly for people with comorbid peripheral neuropathy (113), and being aware of the potential presence of cardiac autonomic neuropathy, which may alter ischaemic symptoms (114).

2.1.4.3.5 Other biomedical risk factors

Other chronic health conditions such as chronic kidney disease (CKD) and autoimmune conditions have been associated with an increased risk of CVD and CHD development. A long-term cohort study of 16,958 people, including 1,210 people with CKD, found the adjusted hazard ratio for CHD in people with CKD was 1.45 (95% CI 1.29-1.62), with hazard ratios for CHD increasing with increasing severity/stage of CKD (115). Additionally, autoimmune diseases have been linked with CHD development, possibly

though the pathological processes related to chronic inflammation (112). A recent database study found the presence of an autoimmune condition increased the risk of CHD, with a hazard ratio of 1.60 (95% CI 1.54-1.66), compared to people without autoimmune conditions (112).

2.1.4.4 Psychosocial

There is increasing acknowledgement of the role of psychological factors as a precedent to CHD. Psychosocial risk factors include poor social support, low socioeconomic status and education levels, mental health disorders and psychological distress. Psychosocial risk factors may act to increase the risk of CHD through eliciting biological changes in response to prolonged stressors, or through modifying behaviours and increasing the traditional risk factor burden (116).

2.1.4.4.1 Social health

Poor social health can result from social isolation, loneliness or lack of social support. A meta-analysis has found that people experiencing loneliness and/or social isolation had an average relative risk of 1.29 (95% CI 1.04-1.59) for incident CHD, compared to people who did not (117). In an Australian cohort study of 11,486 healthy older adults (≥70 years), the hazard ratio for incident CVD was 1.66 (95% CI 1.02-2.70, p=0.04) for social isolation (community activity engagement less than monthly, and contact with 4 or fewer relatives or close friends per month) and 2.05 (95% CI 1.31-3.21, p=0.002) for low social support, although loneliness was not significantly predictive for CVD (1.4, 95% CI 0.95-1.93) and none of the outcomes were significant for fatal or non-fatal MI (118). A review by Lane, Carroll and Yip (1999) summarised that strong social support can help to buffer the effects of psychological distress, reducing its impact on poor outcomes in people with established CHD (119). Group exercise has been associated with increased social support in males and females who were active for at least two exercise sessions per week (120), highlighting that a group exercise training program may be beneficial for a group at risk of social isolation.

2.1.4.4.2 Socioeconomic status and education

The influences of lower socioeconomic status and education levels on an increased incidence of CHD are likely to be multifactorial (33). For example, poorer living and environmental conditions may increase the propensity for some traditional risk factors (121). Additionally, adverse health-related behaviours have been linked to lower health literacy,

which has been associated with lower socioeconomic and educational status (121). Alternately, given the chronic nature of CHD, the association between lower socioeconomic status and CVD burden may be through reverse causation (i.e. people with CHD may be limited in their work capacity, and therefore end up in a lower income bracket (33)). As well as being associated with the primary risk of disease, socioeconomic status may impact secondary prevention. In Australia, a country with universal healthcare, in people with CHD 51% of patients surveyed experienced financial hardship and 12% were unable to pay for medical services, with a similar number unable to pay for medication (52), which may impact on their compliance with appointments and medications. Indeed, in patients with CHD and diabetes in the United States those with financial hardship were significantly less likely to maintain medical appointments and have monitoring tests conducted and experienced a greater degree of vascular morbidity (122). Thus, given the role they can play in CHD, socioeconomic status and education need to be considered when prescribing exercise programs.

2.1.4.4.3 Mental health conditions

The potential pathways for mental health disorders impacting cardiovascular health are through associations with poorer health behaviours, influencing traditional risk factors (119, 123), and through direct pathophysiological effects. For example, with respect to the latter, through acute emotional stress altering autonomic nervous system function, causing a cascade of changes related to a catecholamine surge, which can in turn induce an inflammatory and prothrombotic state (116). The relative risk of CHD development was found to be 1.30 (95% CI 1.22-1.40) in people with depression (124) and 1.41 (95% CI 1.23-1.61) in people with anxiety (125). Alongside the increased risk of CHD in people with anxiety and depression, there appears to be a high risk of anxiety and depression in people with CHD, with 51% of people with stable CHD without a history of MI reporting symptoms of anxiety and 34% reporting symptoms of depression, while those within 6 months of a MI, anxiety symptoms were reported by 57% and depressive symptoms in 23% (126). This is of clinical importance in people with CHD, as increased adverse outcomes were reported in a meta-analysis, with the hazard ratio major adverse cardiovascular events 1.37 (95% CI 1.27-1.48) in males and 1.21 (95% CI 1.12-1.30) in females with psychological factors, such as anxiety and distress (127). Accordingly, recent guidelines for managing chronic coronary conditions have advocated the inclusion of assessments and management for comorbid mental health conditions (128).

Anxiety and depression have both been associated with inactivity (129). Lane, Carroll and Yip (1999) emphasised the interplay between psychological and behavioural factors, highlighting that physical activity and exercise can improve symptoms of depression and anxiety (119). While physical activity is likely to be beneficial for people with CHD and mental health conditions (119), motivational barriers may impact exercise participation in people with mental illness (130), as can symptomology and medication side effects (131), all of which need to be considered when designing exercise programs.

2.1.4.5 Summary

There are a wide range of non-modifiable, behavioural, biomedical and psychosocial factors which increase the risk of CHD development. Many of these risk factors are common to other conditions, such as type 2 diabetes and CKD, which are also independent risk factors for CHD. Notably, having multiple risk factors has a cumulative impact on CHD risk (132). In Australia, 57% of the population over 18 years of age have three or more modifiable risk factors (5), highlighting the need for strong public health programs to reduce the risk of CHD and other chronic conditions.

2.1.5 Comorbidities in coronary heart disease

There is a high prevalence of other chronic conditions in people with CHD, and these include other conditions that can affect multiple body systems (3, 5). In Australian data from 2017-2018, 82% of people with CVD reported having at least one other chronic condition (5). Common comorbidities in patients with CHD include other types of CVD, CKD, musculoskeletal conditions, obesity, and cognitive dysfunction (3, 5, 133-136). While diabetes and mental health conditions are also often comorbidities in people with CHD, they have been discussed in the risk factor section (Section 2.1.4.3.4 and Section 2.1.4.4.3). The presence, or potential presence, of comorbidities needs to be considered when designing exercise and rehabilitation programs for CHD patients, as coexisting conditions can influence a person's ability to engage in some forms of exercise (137, 138).

2.1.5.1 Other vascular disease

Given the shared risk factors between CHD and other vascular diseases, the high prevalence of vascular comorbidities in people with CHD is unsurprising. Swedish data found that between 6% and 14% of people with CHD had experienced a stroke, and between 41 to 69% had hypertension, with the rates dependent on their BMI stratum (134). In a review

of Australian studies of people with CVD, the rate of hypertension ranged from 47-68% and vascular comorbidities different to the index condition were common, though the prevalence ranged widely depending on the baseline health of the population examined (133). Coronary heart disease has also been found to be associated with an increased risk of peripheral vascular disease, with an adjusted hazard ratio of 1.31 (95% CI 1.02-1.66, p=0.032). The presence of other vascular conditions is relevant to exercise training, as these comorbidities may need to be considered in exercise prescription and monitoring. For example, patients who have had a stroke may have balance concerns and start with seated exercises (139), or patients with peripheral arterial disease may experience claudication pain, altering the rests needed during exercise (140).

2.1.5.2 Chronic kidney disease

Chronic kidney disease and CHD are known to share risk factors (5), with CKD being an independent risk factor for CHD (115). In data from the United States, collected from people aged 45 years and older, impaired kidney function (low glomerular filtration rate) was more prevalent in individuals with CHD than in those without CHD (24% vs 8%) (3). Retrospective cohort data from Australia found the incidence of CHD events to be higher in people with CKD than in the general population, with an incidence rate ratio of 1.8 (95% CI 1.7-1.9) in males and 3.4 (95% CI 3.1-3.6) in females (141). Kidney disease was reported as a comorbidity by 6.6% of respondents with CVD in Australia in 2018 (5), while comorbid CVD was reported in 32% of people with kidney disease (5). Poorer kidney function has been linked to an increased incidence of sudden cardiac death in people with CHD over a median of 5.5 year follow up (hazard ratio of 1.11 per 10ml.min^{-1} reduction in estimated glomerular filtration rate, 95% CI 1.06-1.17) (142). The treatment for CKD may necessitate additional considerations for exercise training or physical activity, such as seated/cycling activities for those undergoing dialysis, with moderate intensity suggested as the intradialytic intensity limit (143).

2.1.5.3 Musculoskeletal

Musculoskeletal comorbidities, such as arthritis and joint pain, are common in patients with CHD (3, 135, 137). The prevalence of musculoskeletal comorbidities in people with CHD has been reported as ranging from 27 to 57% (3, 135, 137, 144), and higher than the rates observed in the general population (3, 135, 137). Two American cohort studies found the prevalence of arthritis to be 56-57% in cohorts with CHD, compared to background

population rates of 27-35% in people without CHD (3, 137). In data from the Netherlands, the adjusted odds ratios for back or neck problems, osteoarthritis and rheumatoid arthritis in people with, compared to people without CHD were 1.4 (95% CI 1.4-1.5), 1.4 (95% CI 1.3-1.4) and 1.3 (95% CI 1.1-1.6), respectively (135). Australian data about musculoskeletal comorbidities and CHD are limited, with studies often focussing on the broader category of CVD instead of CHD specifically. One review of multimorbidity in older Australian adults in 2008 found the prevalence of osteoarthritis ranged from 23-58% in people with CVD (133). More contemporary data from 2017-2018 demonstrated that arthritis and back conditions were reported by 49% and 35% of respondents with CVD, respectively (5). International and local data suggest a high proportion of people with CHD and CVD have comorbid arthritis. The presence of arthritis has been found to increase the risk of sedentary behaviour in people with CHD and has been identified as a barrier to exercise (137). Additionally, arthritis may change exercise prescription, with Exercise and Sport Science Australia's most recent guidelines suggesting that low-impact exercise which places low amounts of stress on the affected joints may be best in those with lower extremity arthritis who experience pain (145).

2.1.5.4 Obesity

Being overweight and obese is common in both the general population (5) and in people with CHD (134). Obesity may exacerbate the vascular dysfunction evident in people with CHD; as adipose tissue can perpetuate inflammatory changes through the release of pro-inflammatory adipokines and a reduction in anti-inflammatory adipokines, leading to low-grade, chronic inflammation (146), which can impair endothelial function (1) and contribute to atherosclerosis.

A Swedish study of people with significant CHD found 45% and 21% of patients were overweight and obese (as classified by BMI), respectively (134). Similar rates were found in a Canadian study of patients with CHD, with 48% classified as overweight and 28% classified as obese (147). In 2017-2018 in the general Australian population, the prevalence of overweight or obesity was 67% for adults, with an obesity prevalence of 31% (5). Clinically, the high prevalence of people with CHD being overweight or obese may impact exercise training options due to pain or discomfort with exercise. In American adults, a large cohort study (n=430,912) found that rates of joint pain in people who were underweight, or normal weight (by BMI) were between 32-33%, increasing to 40% when people became overweight, and increasing from 48% to 61% with increasing levels of obesity (148). Meanwhile, arthritis prevalence was 20% in those who were classified as underweight or

normal weight, 27% in those who were overweight, and again increased with increasing levels of obesity from 34% to 46% (148). Clinically, the group with comorbid joint paint experienced a greater probability of functional impairment (36% of people with joint pain, compared to 10% of people without joint pain) (148). Of importance from these data, is that the prevalence of diagnosed arthritis appeared to underestimate reported joint pain in overweight and obese individuals, which may mean the high reported arthritis rates in people with CHD (3, 137) may not necessarily capture the full burden of joint pain in an obese or overweight subgroup of people with CHD.

Current exercise guidelines for people with obesity highlight the need to manage musculoskeletal comorbidities during exercise (149). The effect of buoyancy assists in reducing the weight bearing load through the lower limbs and spine during water immersion (150), which may assist in making exercise more comfortable for those with obesity and joint pain. Indeed, a meta-analysis observed moderate to moderate-to-vigorous intensity water-based exercise for more than 120 minutes per week was found to reduce indices of body fat and increase lean tissue (151), indicating that water-based training is likely to be beneficial in this sub-population of people with CHD who are overweight or obese. Furthermore, exercises supported in water may facilitate improvement in functional exercises, as greater improvements have been seen in some functional outcomes with water-based exercise training compared to land-based training in older males (152) which is important given the higher proportion of people with obesity and joint pain who reported functional impairment (148).

2.1.5.5 Cognitive dysfunction

Almost 40% of people who experienced an MI demonstrated impaired cognition on the Mini Mental State Exam during their index admission (153). While this figure decreased to 25% at 12 months (153), this still represents a substantial association between cognitive dysfunction and CHD. Cognitive impairment was noted as a significant comorbidity in a community living sample of older adults with CHD, with the prevalence of cognitive impairment being 30%, compared to 22% in people without CHD (3). These findings were supported by a meta-analysis, which found that the relative risk of cognitive impairment after MI was 1.49 (95% CI 1.20-1.84) and the relative risk with CHD was 1.27 (95% CI 1.18-1.36), with an increased relative risk for vascular dementia (1.34, 95% CI 1.28-1.39), but not Alzheimer's disease (0.99, 95% CI 0.92-1.07) (136). Some of the cognitive impairment associated with CHD may be related to the impaired cerebral perfusion which has been

observed in people with CHD (154, 155). Impaired cerebral perfusion been associated with impaired cognitive function across a range of cardiovascular conditions (156). In people who were at least 80 years old who had undergone a percutaneous coronary intervention, cognitive impairment (Mini Mental State Exam score below 20) was associated with an increased risk of adverse cardiac events (odds ratio 3.2, 95% CI 1.23-8.29) and cardiac mortality in the 3 years after the intervention, odds ratio 3.8 (95% CI 1.19-12.32) (157). The presence of mild cognitive impairments may necessitate a change in exercise delivery strategies, such as including handouts, ensuring an appropriate communication style (e.g. more feedback, use of multimodal memory aids/music), including friends or relatives in the exercise program, and the choice of exercises used to ensure they are enjoyable and safe, particularly given the association between cognitive impairment and an increase in falls risk (158, 159).

2.1.5.6 Summary

There are many comorbid conditions associated with CHD, potentially affecting a range of body systems. The potential for comorbidities, such as arthritis and obesity, to lead to pain or discomfort with exercise, along with managing comorbidities such as stroke and cognitive dysfunction that are associated with an increased falls risk, highlights the need for careful consideration to be given when designing exercise programs for people with CHD to ensure programs are safe and enjoyable. For example, reduced weight bearing exercises may be more comfortable for those with joint pain comorbidities (148), and programs that allow for adequate support for balance tasks, while still maintaining a challenge, would be appropriate for those with balance impairments. Exercise strategies for people with CHD will be discussed in Section 2.2 and Section 2.3.

2.1.6 The management of coronary heart disease

Coronary heart disease is managed with a broad, multidisciplinary approach to reduce the risk of secondary events or complications, and to optimise patients' physical, psychological and social health. The response during an ACS admission to hospital involves diagnosis, followed by reperfusion (if indicated; either through percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG] or medication), with patients provided with an individualised management plan for secondary prevention involving medication and cardiac rehabilitation (CR) (160). The treatment of chronic CHD involves ongoing medication and lifestyle management, and may involve revascularisation

procedures (PCI or CABG) as part of a staged treatment process or if symptoms persist (128). Current acute and chronic CHD management guidelines emphasise patient centred care, with shared decision making and goal setting (128, 160-163).

2.1.6.1 Medical management

Acute medical management of ACS admissions centres around reperfusion. In suspected ACS presentations 300mg of aspirin is recommended (160), with a $P2Y_{12}$ inhibitor (antiplatelet drug) in those with ACS and at high risk of recurrent events (when not contraindicated), with additional anti-clotting agents, if indicated, during procedures (160).

Long-term medical management is aimed at reducing symptoms of angina and preventing secondary cardiovascular events (163). Angina can be managed acutely with short-acting nitrates, such as glyceryl trinitrate, and prophylactically with long-acting nitrates (163). Medications for secondary prevention vary depending on the length of time from the cardiac event or intervention. In the initial 12 months after a MI the recommended medications include an angiotensin-converting enzyme (ACE) inhibitor (or angiotensin receptor blocker if intolerant to ACE inhibitor), dual antiplatelet therapy (aspirin and a second medication, such as clopidogrel, unless contraindicated), a beta blocker and a statin (164). After 12 months the benefit of beta blockers in people with CHD who do not have heart failure is uncertain (163, 164). Other medications are often used in combination with the above to manage other comorbidities. Medications used in secondary prevention can affect the haemodynamic changes seen with exercise. For example, beta blockers lower heart rate at rest and during exercise (165). This has implications for exercise prescription, as typical age-predicted heart rate maximum equations may not be appropriate for individual patients.

2.1.6.2 Percutaneous and surgical interventions

In the case of an ACS admission to hospital, or for patients with chronic CHD and ongoing symptoms, revascularisation procedures may be indicated. An angiogram is performed to determine disease severity and the number of vessels affected, which, in combination with patient factors, informs whether PCI or CABG is most suitable (128).

A PCI involves inserting a catheter into a peripheral artery (typically radial or femoral) which is then advanced to the base of the target vessel (166). A fine wire is then guided over the stenosed area to guide the remainder of the intervention (166). A balloon is inflated over the target area to open the stenosis, this is then withdrawn and a stent can be placed using a deployment balloon, which holds the vessel open (166). In instances where

the balloon is insufficient to disrupt the plaque, other techniques can be used to modify it, such as atherectomy, laser or lithotripsy balloon to ensure the stent can be fully expanded (166).

The CABG surgical procedure involves the use of one or more of the internal mammary artery, radial artery or a peripheral (saphenous) vein, for revascularising coronary arteries with ≥50% occlusion (167). This procedure is generally used if there is a greater extent or severity of disease, particularly of the left main coronary artery, though a wide range of cardiac and extracardiac considerations guide the decision making process (167). The surgery is most commonly performed via an open chest procedure, though minimally invasive procedures have been used for isolated vessel lesions (167). People who have undergone CABG surgery as an open procedure will have a sternal wound that requires precautions during exercise for up to 3 months during the healing process.

2.1.6.3 Cardiac rehabilitation

In CR there is a multidisciplinary team approach to improve lifestyle factors and medication adherence in a patient centred manner, with the aim of accelerating recovery, halting disease progression and reducing the risk of secondary cardiovascular events (128, 162, 168). Furthermore, CR has been widely regarded as an effective modality for improving health outcomes in people with CHD, with benefits to survival (169-172), reductions in hospitalisations (169, 172) and improvements in function and quality of life (169, 173). Accordingly, guidelines recommend CR for people with CHD, particularly those who have had a recent MI, PCI or CABG procedure, and those with stable angina (128, 162, 163).

The core components of CR services in Australia have been acknowledged as: referral and access to CR, assessment and short-term monitoring (before and after programs), recovery of function and long-term maintenance, behavioural modifications (including lifestyle changes and medication adherence) and evaluation/quality improvement (162). Individualised exercise programs are a key aspect of CR programs and CHD management (128, 161-164, 174-177), with the exercise component discussed in more detail in Section 2.2. Other aspects of CR are incorporated as appropriate for individuals, and can include: education to aid understanding their condition, strategies for self-management, medication management, advice on: smoking cessation, maintaining a healthy diet (nutrition and alcohol intake), reducing sedentary time, managing comorbidities and medical risk factors (including diabetes, hypertension, dyslipidaemia, adiposity), screening for signs of depression or anxiety, and assisting in return to daily activities (161).

A Cochrane review found that only a few studies have reported on the cost effectiveness of CR, with the existing studies reporting variable results, concluding CR may be cost effective (169). In the Australian context, a 2005 study by Briffa et al. found the estimated incremental cost of CR per quality adjusted life year was $42,535 at 12 months (in 1998 Australian dollars), though this reduced to $27,030 when modelling was extended to 3 years (178). More recently, Driscoll et al. (2020) reported CR in Australia has a 99.9% probability of being cost effective at the conventional threshold of cost-effectiveness of $50,000 per quality adjusted life year, and 98.7% probability of being cost effective at a more conservative estimate of marginal productivity ($28,033 per quality adjusted life year), concluding that CR is cost effective in an Australian context, with low costs for high health benefits (179).

While CR is a guideline advocated secondary prevention strategy, the uptake and completion of programs remains sub-optimal (180-183) and this problem persists in Australia. A single-centre Australian study assessing CR uptake found that approximately 40% of people referred to CR attended at their centre, with 45% of those attending withdrawing prior to program completion (184). A more recent analysis of 49,909 separations of patients eligible for CR in one Australian state (South Australia), between 2013-2015, found that 30% of eligible patients were referred to CR and only 28% of those referred attended (183). Finally, an analysis of 39 sites across multiple regions in Australia found a completion rate of 59% in the 2,436 patients engaged in programs during the recording period in 2017 (182).

The gap between established best practice, of having all appropriate patients referred to and attending CR (160, 162), and the challenge of achieving this in clinical practice (182, 183), highlights the need to address barriers to referral and participation, such as developing alternative strategies to increase patient engagement. This is particularly pertinent to exercise and physical activity, which require ongoing adherence for benefits to be maintained (185, 186).

2.2 Exercise in the management of coronary heart disease

Exercise and physical activity are essential components of both CR and secondary prevention for people with CHD (128, 174, 177). Guidelines for exercise prescription for people with CHD (174-176), apply the same principles to those recommended in the general population (84), but are refined to reflect patients' cardiovascular disease status. The benefits of exercise in people with CHD range from increased survival (187) through to

improvements in risk factors (188), aerobic capacity (187), function and quality of life (173, 189, 190). While there are many established benefits of exercise in people with CHD, adherence to exercise and physical activity is often sub-optimal and there are several identified barriers to exercise participation, ranging from time and motivation through to comorbidities.

2.2.1 Exercise prescription for people with coronary heart disease

Historically, exercise prescription for people with CHD focussed on aerobic training at low to moderate intensities (191, 192). With new evidence for other exercise modalities emerging, guidelines have evolved to incorporate increases in intensity for aerobic activity, and resistance training has been included as a core component (174, 175). Aerobic exercise involves repetitive rhythmic movements of large muscle groups, such as walking or cycling, which draw on aerobic metabolism for energy production (193), while resistance exercise involves muscle contraction against an external force, like lifting weights or performing a movement against an elastic band (194).

A key benefit derived from aerobic exercise training is increased aerobic capacity, measured as peak oxygen consumption (VO_{2peak}) (188), with a higher VO_{2peak} (195) and greater increases in VO_{2peak} as a result of exercise training (187) being found to be associated with increased survival. A meta-analysis of aerobic endurance training has found reductions in SBP and LDL-C, with increases in HDL-C (188). Other studies have found that continuous aerobic training can improve endothelial function (196-200), suggesting there are a wide range of potential benefits from this modality.

Resistance training in people with CHD has been supported by a recent scientific statement by the American Heart Association, finding the modality safe and effective for people with stable CVD (194). Meta-analyses examining the role of exercise training modalities in people with CHD found that aerobic and resistance exercise training produced similar benefits to aerobic capacity (VO_{2peak}) (201, 202) and quality of life outcomes (202). While few studies have examined the impact of resistance training alone on endothelial function in people with CHD, Vona et al. (2009) observed that flow mediated dilation (FMD) increased with resistance training (199). Furthermore, greater quadriceps strength has been associated with a lower mortality risk in people with CHD (203). This is in line with the findings of a meta-analysis in the general population, where the performance of muscular strengthening activities was associated with a 15% reduction in the risk of all-cause mortality

(204). The benefits seen with resistance training in people with CHD supports the inclusion of resistance exercise training in programs for people with CHD.

As there are survival benefits from increasing aerobic capacity (187) and muscular strength (203), combined aerobic and resistance exercise training (combined training) is often recommended in CR (174). Early meta-analyses found that combined training increased exercise test duration more than aerobic training alone (201, 205), while the most recent meta-analysis, by Fan et al. (2021), found a greater increase in VO_{2peak} from combined training than aerobic training alone (mean difference +1.26ml.kg^{-1}.min^{-1}, 95% CI 0.41-2.90ml.kg^{-1}.min^{-1}) (202). Furthermore, muscular strength changes were found to be greater with combined training than aerobic training (201, 205) and fat free mass, left ventricular ejection fraction and global quality of life outcomes increased, while body fat percentage and trunk fat decreased with combined training compared to aerobic training (202, 205). These positive changes occurred without an increase in training program withdrawals (205), indicating that combined aerobic and resistance training should be included for patients with CHD.

Research into exercise training types in people with CHD has translated into clinical recommendations. A recent position statement from the Cardiac Society of Australia and New Zealand provides a clinical guideline for exercise and physical activity prescription in CR, and incorporates both aerobic and resistance exercise training (174). Additionally, these guidelines highlight the importance of exercise programs being patient-centred and individualised (174). Other recommendations include using an assess-prescribe-adjust-re-assess cycle for progressing programs, with prescription design following the FITT-VP (frequency, intensity, type, time, volume and progression) principles (174). In addition to exercise recommendations, the position statement encourages the reduction of sedentary behaviour (174), which international guidelines support (128, 175).

The detailed recommendations for aerobic training are (174):

- Frequency: at least three sessions per week (if performing high intensity training 2 or more sessions should be high intensity)
- Intensity: moderate to high intensity (55-90% of maximum heart rate, or rating of perceived exertion 12-16 on the Borg Category Scale)

- Time: sessions of more than 30 minutes of aerobic activity, this can be split into smaller bouts and then progressed towards 30 minutes for deconditioned patients
- Type: a variety of exercises that use large muscle groups, such as walking, swimming, rowing, cycling can be used, and upper limb ergometry can be used if there are lower body limitations
- Volume: at least 150 minutes per week, with more than 210 minutes recommended for greater benefit
- Progression: slow and gradual (5-10% every 1-2 weeks), increasing duration up to the 30 minutes per session before increasing intensity.

The detailed recommendations for resistance training are (174):

- Frequency: 2-3 sessions per week with, ideally, 2 days between sessions
- Intensity: moderate to high intensity (50-80% of one repetition maximum, or rating of perceived exertion of 5-7 on the Borg Category Ratio Scale
- Time: at least 20 minutes per session, and each repetition should be more than 4 seconds (with a 1:3 ratio of concentric/ muscle shortening to eccentric/ muscle lengthening within each repetition)
- Type: a range of major muscle groups, can be whole body exercises, or exercises where the muscle crosses one or two joints, ideally done bilaterally for limb exercises. The resistance can be from body weight, weights machines, elastics or free weights
- Volume: each session volume of 15-36 repetitions per muscle group (up to 3 sets of 8 to 15 repetitions)
- Progression: progress volume and intensity prior to progressing other factors e.g. increase repetitions to 15 prior to increasing intensity (and lowering reps).

International guidelines largely concur with the Australian position statement, supporting at least 150 minutes per week of moderate to high intensity exercise (128, 163, 175), or 75 minutes of vigorous intensity exercise (128), with the European guidelines specifying the activity should be on at least 5 days per week (163). Additionally, European guidelines use the FITT approach, with an additional consideration of time from last meal

(175). Resistance training has some additional guidance in the European secondary prevention guidelines, which proposes using 40-80% of one repetition maximum for the lower body and 30-70% of one repetition maximum for the upper body for exercise prescription, with a target of 12-15 repetitions in one set (175).

As both aerobic and resistance exercise components are recommended in the guidelines, methods for incorporating these into CR sessions need to be considered. Strategies undertaken have included separate aerobic and resistance training sessions (206), segmented training sessions, with an aerobic or resistance block, followed by the other (207, 208), or circuit training exercise (209), involving alternating stations of aerobic and resistance exercises. Gym-based circuit training involving alternating aerobic and resistance exercises has the benefit of allowing aerobic and resistance exercise to occur within the same session, and has been found to provide a range of health benefits, including increased exercise test duration or maximal metabolic equivalent (209-212), endothelial function (209, 213, 214), left ventricular ejection fraction and diastolic function (210), and muscular strength (210-212) and VO_{2peak} (211, 212), in populations with heart failure, type 2 diabetes and CHD. Given that a lack of time is a common barrier to exercise in people with CHD (184, 215), selecting an efficient and effective training program may assist with adherence.

2.2.2 Effect of exercise or exercise based cardiac rehabilitation on morbidity and mortality in coronary heart disease

Exercise-based CR has been found to have favourable impacts on cardiovascular mortality and morbidity in people with CHD (169). Further, meta-analysis data from a recent Cochrane review reported significant reductions in cardiovascular mortality (overall risk ratio 0.74, 95% CI 0.64-0.86), MI (overall risk ratio 0.82, 95% CI 0.70-0.96) and all-cause hospitalisation (overall risk ratio 0.77, 95% CI 0.67-0.89) in people with CHD who underwent exercise-based CR (216). A greater reduction was seen for MI risk and cardiovascular mortality with longer duration (>36 months) follow up (216). Supporting the use of longer duration training programs in people with CHD, Taylor et al. (2017) investigated the effects of exercise dose on survival in people with CHD following an extended community-based exercise-based CR program with follow up lasting a median of 14 years (185). They found that supervised exercise for more than 36 months reduced mortality by one third compared to programs with a duration shorter than 36 months, even when baseline characteristics,

comorbidities and survivor bias were accounted for (adjusted HR 0.67, 95% CI 0.47-0.97) (185).

There has been some debate whether CR programs in the modern treatment era still confer survival benefits, with one meta-analysis finding that studies after 2000, conducted after the introduction of increased revascularisation and improved medical therapies (217), no longer conferred survival benefits (218). However, another meta-analysis which only including studies recruiting from 1995 onward, found significant survival benefits (171), as did an updated Cochrane review for cardiovascular mortality (169, 216). Furthermore, a recent large cohort study (26,171 people who participated in CR, 57,516 people who did not participate) found CR to reduce mortality with an adjusted hazard ratio of 0.68 (95% CI 0.65-0.71) (219), indicating CR programs are still effective in the modern treatment era.

In addition to exercise-based CR, physical activity changes over time have been linked to survival in people with CHD (186, 220). Over a median 15.7 years follow up, people with CHD who met physical activity guidelines, or had high levels of physical activity, had a lower risk of adjusted all-cause mortality than people with CHD who remained inactive over the study period (adjusted hazard ratio 0.64, 95% CI 0.50-0.83) (220). A smaller reduction was seen in those who maintained low levels of physical activity (below guideline levels) over time (adjusted hazard ratio 0.81, 95% CI 0.67-0.97), compared to inactive people (220). In terms of cardiovascular mortality, benefit was only seen in those who maintained high levels of physical activity over time, and in those who were inactive initially but who subsequently transitioned to high levels of physical activity (220). A meta-analysis of physical activity trajectory data found in people with chronic CHD that, compared to inactive people who remained inactive, those who were active over time had a 40% lower risk of mortality, those who became active had a 31% lower mortality risk and those who decreased activity over time had no difference in risk (186). These findings have been supported by a singular baseline assessment of physical activity levels at study entry in people with chronic CHD who were then followed over a median 3.7 year period (221). Total mortality was approximately 30% lower in people with CHD who were the most active, compared to those who were in the lowest tertile for physical activity when adjusted for baseline covariates, with similar findings for cardiovascular mortality (adjusted hazard ratio 0.71, 95% CI 0.58-0.88) (221).

Increases in cardiorespiratory fitness (aerobic capacity), as expressed by VO_{2peak} appear to be associated with survival improvements in people with CHD. Patients

undertaking a CR program who improved their VO_{2peak} had lower mortality than people who did not (13% vs 22%) (187). Further to this, those who increased their VO_{2peak} by at least 2.5 $ml.kg^{-1}.min^{-1}$ (high responders) had improved survival compared to those who were low responders (<2.5 $ml.kg^{-1}.min^{-1}$ improvement) and non-responders (≤0 $ml.kg^{-1}.min^{-1}$) (187).

In summary, these studies suggest that exercise-based CR, increases in aerobic capacity and high levels of physical activity reduce mortality and some adverse outcomes, such as hospitalisation, in people with CHD and that the degree of benefit may be related, in part, to the extent of training-related changes in cardiorespiratory fitness. Furthermore, longer duration programs and those resulting in sustained increases in physical activity had better survival outcomes, demonstrating the importance of long-term exercise and physical activity for risk reduction for people with CHD. This highlights the need for effective CR programs with good adherence to support ongoing exercise and health.

2.2.3 Effect of exercise on health-related outcomes in people with coronary heart disease

Exercise training can provide many benefits to function, health and risk factors, which likely contribute to the improvement in survival outcomes seen with exercise-based CR. This section outlines the impact of exercise on aerobic capacity, muscular strength, vascular function, body composition, blood pressure, blood profile and cerebrovascular outcomes.

2.2.3.1 Aerobic capacity

Aerobic, resistance and combined exercise training have all been found to increase aerobic capacity, measured as VO_{2peak}, in people with CHD (187, 188, 201, 202). Meta-analyses in people with CHD have found that aerobic endurance training increased VO_{2peak} (mean difference +3.47$ml.kg^{-1}.min^{-1}$, 95% CI 2.41-4.53$ml.kg^{-1}.min^{-1}$) (188), with comparable benefits from aerobic and resistance training (+21% and +16%, respectively) (201). Furthermore, there may be an added benefit from combined aerobic and resistance training, over aerobic exercise training alone (+1.26 $ml.kg^{-1}.min^{-1}$, 95% CI 0.41-2.12$ml.kg^{-1}.min^{-1}$) (202).

Aerobic capacity at baseline entry to CR was associated with all-cause and cardiovascular mortality risk over a median 5 year follow up, with a 1 $ml.kg^{-1}.min^{-1}$ higher VO_{2peak} associated with a 15% reduction in all-cause mortality, and this relationship was maintained when the influence of improved secondary prevention medication prescription was accounted for (195). More recently, the degree of VO_{2peak} change within a program was found to vary

between individuals, when an aerobic exercise dominated CR program led to improvements in most (77%), but not all, patients with CHD attending CR in a large single centre study (n=1,171) (187). Approximately 38% were high responders (>2.5 $ml.kg^{-1}.min^{-1}$change in VO_{2peak}), 39% were low responders (0 to ≤2.5$ml.kg^{-1}.min^{-1}$ change in VO_{2peak}) and 23% were non responders (<0 $ml.kg^{-1}.min^{-1}$ change in VO_{2peak}) (187). The high responders experienced greater survival benefits, compared to both low and non-responders (8% mortality, compared to 17% for low responders and 22% for non-responders) (187). Given the substantial difference in survival outcomes between response categories, the lack of universal improvement with aerobic training, and the positive difference in VO_{2peak} seen though meta-analysis for combined training (202), modifying training programs based on training responses, or trialling a combined aerobic and resistance program initially may be advantageous. This is supported by data from young, healthy people, which demonstrated, in a crossover study of aerobic and resistance training, that only 4% of people had no change, or negative change in VO_{2max}, in response to both aerobic training and resistance training (222), indicating that if no improvement was seen with one modality, then the other should be considered.

2.2.3.2 Muscular strength and function

A meta-analysis found that both lower and upper body muscular strength were increased with either resistance training alone, or in combination with aerobic training, compared to a control group performing usual activities in people with CHD (201). However, Fan et al. (2021) noted the difficulty in making comparisons between training types due to the variety of assessment methods used, but agreed that aerobic and resistance training generally had favourable effects on muscular strength compared to aerobic training alone (202). Increased quadriceps strength in relation to body weight has been associated with improved survival in people with CHD (203), and in the general population muscle strengthening activities was found to reduce the risk of all-cause mortality by 15% (204), indicating the clinical importance of this outcome.

In addition to increases in strength, improvements have been reported in functional outcomes with exercise training in people with CHD. In one study, 12 weeks of combined training, with low or high load resistance, three times per week was compared to aerobic training alone (223). The high load, low repetition resistance training program provided greater benefits to gait speed, arm strength, Up and Go Test time, compared to the aerobic training group (223). The lower load, high repetition program provided greater benefit to Up

and Go Test time and the sit to stand test than aerobic training (223). All groups improved six-minute walk test time, postural balance, heel raises and lower limb flexibility (223). These functional improvements are important, as impairments in static and dynamic balance are associated with falls risk in people with CHD (224). Given that optimising function is a key aim of CR (162), and that outcomes of tests such as the Up and Go Test are linked with survival in older adults (225), these findings further highlight the clinical benefits of exercise training in people with CHD.

2.2.3.3 Vascular function

Vascular endothelial dysfunction is a key process in the development of CHD (discussed in Section 2.1.1) (1, 209, 226). Flow mediated dilation is used to assess endothelial function non-invasively in peripheral arteries (227) and this assessment has been shown to be at least partially mediated by NO (15). People with CHD have been found to have impaired (lower) FMD compared to age-matched people without CHD (209, 228, 229), with the degree of impairment associated with the severity of coronary lesions (226). Persistently impaired endothelial function in people with newly diagnosed CHD over six months, despite otherwise optimal management of risk factors, is associated with an increased risk of cardiovascular events (adjusted hazard ratio 2.9, 95% CI 1.5-6.2) (230). A meta-analysis supported the association of impaired FMD and adverse outcomes in CVD, finding in people with CVD for per 1% increase in percent FMD the risk ratio is 0.84 (95% CI 0.79-0.88) for cardiovascular events (231).

Flow mediated dilation can be improved with exercise-based CR, with a meta-analysis of 18 studies finding a moderate-sized standard mean difference of 1.04 (95% CI 0.76-1.31), in people with CHD (200). While study heterogeneity and inconsistency were high, sub-analyses did not indicate a concern of bias (200). The adaptation in endothelial function with exercise training is likely to be mediated by repeated exposure to transient increases in shear stress (232, 233). As explained in Section 2.1.1, shear stress occurs as the result of the friction of blood on the endothelium (12) and is augmented from the increased blood flow that occurs during exercise (232, 234, 235), or from other stimuli that increase blood flow to the periphery, such as a local limb heating (236).

Shear stress stimulates the release of NO and other vasoactive substances, inducing vasodilation (13, 232). Over time, repeated bouts of exposure lead to adaptation in the artery (233). Initially this is a functional change, and the endothelium increases the expression of eNOS (232). This has been demonstrated in the internal mammary arteries of

people with CHD who undertook exercise training prior to a CABG procedure (196). After an initial increase in functional response to the increase in shear stress, vessel remodelling may occur (233, 237). Given the association with disease severity and survival, exercise-induced improvements in endothelial function are an important target for training programs in people with CHD. Taking into consideration the acute differences in shear stress during different types of exercise (235), research is required to determine if exercise training can be tailored to maximise any possible benefits to endothelial function.

2.2.3.4 Plaque volume

Invasive imaging studies have demonstrated a relationship between physical activity and plaque progression and structure (238, 239). In one study, integrated backscatter intravascular ultrasound, which is used to determine the composition of plaques, was conducted at the time of PCI and after 8 months, with patients randomised to attend a higher frequency (twice or more weekly) CR program and perform at least 9,000 steps per day, or a fortnightly CR program (one or more visits fortnightly) with a ≥6,000 steps per day target (239). Despite the different prescribed programs, there was a similar change in step count and VO_{2peak}, and the number of CR sessions attended was similar between groups (239). Both training groups significantly reduced plaque volume over time (-9% in intensive, -5% in control) (239). Due to the compliance issues with the training programs, the cohorts were re-analysed around the split of the median step count (7,000 steps per day) (239). When separated into more active and less active groups, plaque volume was significantly reduced in both groups, with the more active group significantly reduced compared to the inactive group (-13% vs -4%). The more active group also had a reduction in lipid and fibrous plaque volume and an increase in the percent calcified volume (a more stable plaque type), while these changes were not seen in the less active group (239). Physical activity and LDL-C were univariate and multivariate predictors for plaque volume change, and the presence of diabetes approached significance (239). Physical activity was the only variable associated on both uni- and multivariate analysis for lipid volume, with ACS classification approaching significance and HDL-C approaching significance in the univariate analysis only (239). Another study utilising radiofrequency intravascular ultrasound compared 12 weeks of high intensity aerobic interval training (90% of peak heart rate) to moderate intensity continuous training (70% of peak heart rate) and found both training interventions reduced plaque burden by approximately 11% and significantly reduced plaque necrotic core (238). This occurred alongside a tendency for brachial artery FMD to increase in both groups (238).

These findings support the use of physical activity in improving plaque profiles and reducing plaque burden. The stabilisation of the plaque profile in non-stented segments provides a potential mechanistic explanation for the improvement in event free survival in patients who performed a cycling intervention, compared to stenting, over the course of 12 months (240) and highlights the value of exercise interventions for improving cardiovascular disease risk in people with CHD.

2.2.3.5 Body composition

Changes in body composition as a result of participation in CR have been variable. A large (n=19,136) registry study in Sweden found that attending CR led to reduced weight gain at 12 months, compared to non-attenders, although while the effect was statistically significant the clinical relevance was uncertain (CR +0.0±5.7kg vs 0.3±5.7kg) (241). Another study found that a combined aerobic and resistance training program performed alongside traditional CR education (length of program dependent on baseline assessment of cardiovascular risk, between 12-31 sessions), found no changes in weight in patients with CHD, although a specific cohort who were post-MI increased weight by a small amount (+1.4kg), while there was no significant change in BMI, visceral body fat or waist to hip ratio (242). Theodorou et al. (2016) compared aerobic, resistance and combined exercise training in people with chronic CHD and found after 4 months of training, weight was lower in the aerobic and combined exercise groups and by 8 months of training it was reduced in all the training groups (-3.2%, -2.5% and -4.5% with aerobic, resistance and combined training respectively) (243). Body fat was reduced by 4 months with all training types (-4.3%, -3.4%, -3.1% with aerobic, resistance and combined training respectively), while BMI was lower with combined training at 4 months, and changed in all training groups at 8 months (243). The benefits observed on body composition may vary with the assessment outcome utilised. For example, assessments of body composition that can delineate changes in tissue types, such as dual energy x-ray absorptiometry (DXA) scans, may be able to pick up more subtle changes. A meta-analysis of DXA data found a weighted mean difference of +0.88kg (95% CI 0.39-1.36kg) for lean tissue and a 2.3% loss of body fat after combined aerobic and resistance training, compared to aerobic training, in people with CHD (205).

Diet can impact the changes seen in body composition. Aerobic interval training for 12 weeks led to a 1.6% reduction in weight, however dietary intervention over the same time period resulted in a 10.6% reduction in weight, suggesting exercise strategies may be more effective when combined with dietary input (244).

It appears, particularly for shorter duration exercise programs, that measures of body composition that can discern changes in tissue type may be able to better ascertain any benefits to body composition. Additionally, dietary intervention in tandem with exercise appears to have a greater impact on body composition than exercise alone.

2.2.3.6 Blood pressure

Hypertension is prevalent in people with CHD (134, 245) and associated with an increased risk of adverse outcomes (246). A meta-analysis of moderate to high intensity aerobic training interventions for people with CHD found a reduction in SBP of 4mmHg (205). A recent registry study in the United States (n=31,885) investigated the impact of 12-36 sessions of Phase II CR on blood pressure (247). Cardiac rehabilitation was found to reduce SBP and DBP by a small (1mmHg), but statistically significant amount and 74% of attendees achieved a blood pressure <130/80mmHg by the end of the program (247). A higher number of sessions attended was associated with greater improvement in DBP (247). Furthermore, people with Caucasian or Asian heritage reduced SBP and DBP, while people with Black or American Indian heritage did not and people identifying a Hispanic ancestry only demonstrated improvements in DBP (247). A single centred trial in people with stable CHD and hypertension (n=74) found that aerobic exercise-based CR was effective for reducing SBP and DBP in patients who were obese (BMI>30kg.m^2) and non-obese (SBP -22mmHg obese, -15mmHg non-obese; DBP -11mmHg obese, -9mmHg non-obese) (248). Differences from the registry study may be related to differences within the patient cohorts, with the single centred study having a higher proportion of females, younger participants and higher baseline blood pressure readings (248).

Findings of improved blood pressure with exercise are consistent with a large-scale meta-analysis of 270 trials (n=15,827) across a range of populations which investigated the impact of different exercise training modalities on blood pressure and found that aerobic training reduced SBP on average by 4.5mmHg, while in people with hypertension the reduction in SBP with aerobic exercise was 8mmHg (249). In people with hypertension, combined aerobic and resistance training reduced SBP by 11mmHg, compared to an 8mmHg seen with aerobic training alone (249). These findings suggest exercise training in people with CHD reduces SBP and DBP, and there may be greater reductions in people with hypertension, which is common in people with CHD (133, 134).

2.2.3.7 Blood profiles

Current lipid management and CHD guidelines emphasise the importance of LDL-C as the leading atherogenic lipoprotein (250-252). A meta-analysis of moderate to high intensity aerobic training interventions for people with CHD found a reduction in LDL-C (mean difference -5.5mg.dL^{-1}), an increase in HDL-C (mean difference +3.8mg.dL^{-1}), without significant changes in triglycerides or total cholesterol (188). Of note, three of the four studies included in the meta-analysis were 24 weeks long (188), so the effects of short-term training interventions are unclear. A trial by Theodorou et al. (2016) compared aerobic, resistance and combined exercise training in people with CHD, sampling at four and eight months, and found the only significant changes at four months were in triglycerides in the aerobic and combined training group and HDL-C in the combined group (243). By eight months changes were apparent in total cholesterol, LDL-C and HDL-C in the aerobic and combined training groups, and triglycerides in all the training groups (243).

Another aspect of the blood profile that can be a marker of inflammation and cardiovascular risk is C-reactive protein (253). High sensitivity C-reactive protein reduced with aerobic, resistance and combined exercise training at four months, and remained lower than baseline values after eight months of exercise training in people with CHD, while the control group did not demonstrate any changes (243). A meta-analysis has found CR reduced high-sensitivity C-reactive protein (-1.81mg.L^{-1} 95% CI -2.65 to -0.098), however there was high heterogeneity in the analysis and benefits appeared to be reduced with longer duration follow up (254).

These studies suggest it may take an extended period of exercise training (≥12 weeks) for changes in the lipid profile to become apparent in people with CHD, and it may take up to eight months for any changes in LDL-C to become apparent, highlighting the need for exercise strategies to promote ongoing exercise in this population. Conversely, high sensitivity C-reactive protein, an inflammatory marker, appears to reduce within weeks of starting exercise training.

2.2.3.8 Cerebral outcomes

As highlighted in Section 2.1.5.5, there is a link between cognitive impairment and CHD, with a meta-analysis finding the odds ratio for developing cognitive impairment or dementia in people with CHD is 1.45 (95% CI 1.21-1.74) (255). Another meta-analysis supported these findings, finding an increased risk of cognitive impairment and vascular

dementia, particularly in people who have had an MI (136). Additionally, adverse structural changes have been observed in cerebral grey (256, 257) and white matter (258), as well as reductions in cerebral perfusion (154, 155, 259). Furthermore, in people with severe CHD (triple vessel, or left main coronary artery), two thirds were found to have silent intracranial stenosis detectable by transcranial ultrasound (260), highlighting that people with CHD commonly experience atherosclerosis in other vascular beds apart from the coronary circulation.

Reduced cerebral perfusion may contribute to cognitive impairments in people with CHD. In people at high risk of CHD, who did not have cognitive impairments, middle cerebral artery blood velocity (MCAv) was reduced at rest and during exercise, and associated with reduced language processing performance (261). Additionally, in older adults, an inverse relationship between left MCAv and global cognitive decline has been observed (262). With progression to overt CVD, reduced cerebral perfusion, assessed through magnetic resonance imaging, was associated with cognitive dysfunction (156) .

Corrections of cerebrovascular perfusion deficit may be able to reverse some of the adverse changes in cognition. When cerebral hypoperfusion was improved after CABG or valve replacement in people with chronic cardiac conditions, an increase in regional cerebral blood flow was associated with an improvement in psychomotor speed (263). While global changes in MCAv were not seen with exercise-based CR (259), regional changes in cerebral perfusion have been demonstrated, particularly in areas of reduced perfusion at baseline (155), indicating more localised changes may occur, and some recovery was seen in areas where adverse changes to grey and white matter in the brain had been noted (256, 258). A longer duration (48 week) exercise program in people with CHD was associated with an improvement in executive function and verbal memory (264). However, existing adverse changes in white matter, such as hyperintensities in cholinergic tracts, attenuated the improvement in executive function seen with exercise training, despite similar improvements in VO_{2peak} (264). Positive findings were observed during a shorter duration, 12 week program in people with CVD (specifically MI, CHD, hypertension or heart failure diagnoses) referred for CR, with improvement in attention-executive-psychomotor and verbal memory aspects of cognition (265).

Some of these improvements in cognition and regional perfusion may relate to upregulation in cerebrovascular function. In the cerebral circulation, NO and shear stress have been implicated in cerebrovascular responses to environmental stimuli, such as neurovascular coupling (266, 267). In the peripheral circulation, repeated increases in shear

stress and the resultant increases in NO and other vasoactive substances are thought to mediate improvements in endothelial function (15, 233). Furthermore, peripheral arterial function changes may be linked to cerebral responses and cognition. A three-month long study of exercise-based CR in people with CHD found increased endothelial function (measured through peripheral artery tonometry) over time was associated with an improvement in overall cognition and processing speed (268).

During acute exercise, increases in MCAv have been observed in people at high risk of CHD (261), which may provide an increase in cerebral shear stress. While exercise increased MCAv in people at high risk of CHD, the increase was attenuated compared to healthy controls (261), which may indicate the MCAv and cerebral shear stress response to exercise may be diminished in people with CHD (268). Further research is required to work out how to optimise cerebral shear stress for people with CHD to maximise improvements in cerebrovascular function and prevent cognitive decline.

2.2.3.9 Summary

Exercise is a key component of CHD management, with the main modalities being aerobic, resistance and combined exercise training. The literature suggests greater benefits may come from combined training and contemporary CHD guidelines reflect this in their recommendations. Exercise training has been found to benefit aerobic capacity, muscular strength and vascular function, and improvements in these outcomes have been associated with increased survival in people with CHD. Additionally, benefits have been seen in body composition and blood profiles, with greater changes seen with longer duration (more than four month) programs. Caloric restriction provided greater benefit to body composition than training alone, highlighting the role of a multidisciplinary team for optimising risk factors in people with CHD. While exercise training was generally found to have favourable impacts on cognition and regional cerebral perfusion, little research has been done in this area and further research is required to optimise training interventions for these outcomes.

2.2.4 Adherence to exercise and physical activity in people with coronary heart disease

Long-term increases in physical activity have been associated with improved outcomes in people with CHD (186, 220), yet a variety of international cohorts have reported that the proportion of the population meeting exercise and physical activity guidelines was below 30% (269-272). Even when studies used a more relaxed ‘active’ criterion, of achieving

at least 150 minutes per week of any intensity activity, the proportion of participants who meet this criterion remained at or below 50% (273-275). While physical activity rates improved with exercise training and were maintained for 12 months in some studies of people with CHD (271, 273), there were still large residual proportions of the cohorts who remain sedentary (49% (271), 33% (273)). Conversely, a study of objectively measured physical activity found a reduction in the number of people meeting at least 90 minutes of moderate intensity physical activity per week between 2 months and 12 months post-CR (71% vs 49%), although the difference in those achieving the guideline recommendation of at least 150 minutes of moderate intensity physical activity was not significantly different between groups (54% at 2 months, 41% at 12 months) (276).

The criteria for meeting physical activity goals have not been well specified throughout the literature, and studies have adopted different approaches for both measuring physical activity and defining physical activity goals, which may explain the variety of findings between studies. Additionally, the disparate findings may reflect differences in study populations as age (271) and comorbidities (273, 277, 278) are known to reduce physical activity levels in people with CHD. Regardless of the difference between studies in the physical activity criteria applied, regular physical activity has been shown to be consistently sub-optimal, with between 33-80% of people with CHD failing to achieve physical activity targets (269-273).

While the proportion of people with CHD engaged in regular exercise is low, this is not solely due to an unwillingness to exercise. A large cohort study across Europe in people with CHD (n=8,261) observed that while only 34% of participants reported performing at least 30 minutes of planned physical activity five days week (no intensity specified), 58% of participants not currently exercising reported wanting to become more active (275). These findings highlight a major opportunity for exercise professionals to assist in increasing physical activity levels in people with CHD and highlight the importance of developing exercise and physical activity strategies that reduce barriers to exercise to facilitate an increase in participation.

2.2.5 Potential barriers to exercise and exercise-based CR in people with coronary heart disease

Most of the literature examining reasons for non-participation in exercise in people with CHD is related to non-participation in, or withdrawal from, exercise-based CR programs. As this project is focussed on an exercise training intervention, rather than a multidisciplinary CR

program, the literature has been reviewed in the context of potential barriers to exercise training. The key groupings for barriers to participation identified as affecting people with CHD and discussed below are: CR program, logistical, intrapersonal and clinical factors (181).

2.2.5.1 Cardiac rehabilitation program factors

Traditional outpatient, gym-based, group exercise may not suit all people with CHD. One study reported that the reasons for withdrawal from CR included patients preferring to exercise in a local community gym or closer to home, patients not feeling benefits from the program or disliking the program (181). A dislike of aspects of group programs, such as listening to the problems of others, and not feeling comfortable talking in groups has been identified (184), although these issues likely relate predominantly to the educational aspects of the program. Participants raising issues with traditional gym-based group CR not suiting them emphasises the need for alternative exercise strategies or settings to be investigated to support greater adherence to exercise participation in CR.

2.2.5.2 Logistical factors

The key logistical issues highlighted in the literature include time pressures and transportation or distance issues. Lack of time overall (184, 215), due to work (181, 184, 279) or family commitments (215, 279) have been raised as barriers to outpatient hospital or primary care centre-based training by people with CHD. Access to transportation (181, 184, 279, 280), the distance required to travel (184, 280, 281), and rural or inaccessible locations (280) have been other issues raised. Weather and environmental factors have also be found to affect exercise participation in an Australian study (215). These points emphasise the importance of developing individualised programs for patients with CHD that have more flexibility and fewer travel requirements than traditional CR, such as telehealth, local community programs or sessions delivered outside of work hours.

2.2.5.3 Intrapersonal factors

Motivation and self-efficacy have been identified as significant factors affecting exercise participation in people with CHD (280), while stress from a broad range of causes is associated with program withdrawal (181).

Patients who felt they were managing their condition well (280) and those who felt they did not need CR (181, 280) or were not ‘sick’ enough for the intervention (181), were

more likely to withdraw from programs, as were those with higher self-efficacy (280). Research needs to be undertaken to determine if these participants went on to independent exercise after withdrawing from the group programs, or if they could benefit from a higher intensity training approach.

People with lower self-efficacy were less likely to participate in an exercise-based CR program to begin with (280), and depression has been associated with poorer exercise self-efficacy in people with CHD (215). Cohort studies of people with CHD found self-efficacy was relevant to exercise behaviour change in the short-term (282, 283), although this relationship attenuates over time, particularly for women (283). Exercise physiologists and physiotherapists are well suited to supporting and encouraging exercise self-efficacy in the initial stages of CR to assist in engaging people in programs.

Motivation to perform exercise was a significant factor affecting participation and withdrawal from exercise-based CR (181, 215, 279, 282). Self-determined motivation was associated with exercise behaviour at 12 months (282). A component of self-determined motivation is intrinsic motivation, from finding enjoyment in the behaviour (282), which has also been identified as key factor for improving exercise adherence in a review of factors influencing exercise adherence in people with chronic disease (284). Furthermore, motivation to exercise can be improved over time with an exercise and education intervention in people with CHD, with the authors suggesting health professionals should consider the addition of new exercise options or music to make training sessions more enjoyable (215). These findings highlight the influence of motivation on exercise adherence and the importance of strategies to keep participants motivated to exercise, such as individually tailored exercise programs, that are well-tolerated and enjoyable.

In summary, lower exercise self-efficacy has been associated with poor uptake of exercise programs and behaviours, while lack of motivation has been a noted barrier in a range of studies. Exercise and education programs may be able to increase motivation to exercise (215), and exercise professionals are well-placed to support the development of exercise self-efficacy. Furthermore, ensuring there are exercise options that the participants find enjoyable is also likely to improve adherence (284).

2.2.5.4 Clinical factors

There is a high prevalence of comorbidities in people with CHD, as discussed in Section 2.1.5. General health issues (215) and comorbidities (181, 279) have been identified

as barriers to exercise-based CR participation. Aside from general health, other factors associated with non-participation and withdrawal from exercise-based CR, or low exercise participation, include smoking (280), a fear of falling or being at risk of falls (278), musculoskeletal pain (137, 144, 181, 277), reduced functional capacity and exercise tolerance (280, 285), type 2 diabetes (280), and more severe disease (280). In contrast, having had a CABG procedure was associated with increased participation (280). The impact of elevated BMI or obesity on exercise participation has been variable in the literature, with reductions in exercise or CR participation found in some (280, 285), but not all (286) studies. This section will outline in more detail the potential barriers of being at an increased risk of falls and musculoskeletal comorbidities, as these factors are present in a high proportion of people with CHD (3, 135, 137, 277) and are strongly associated with reduced exercise participation (144, 277, 278).

Falls risk

A meta-analysis of studies examining the prevalence of falls in people with cardiovascular conditions demonstrated that people with CHD were at greater risk of falling, with an adjusted odds ratio of 1.13 (95% CI 1.05-1.23) compared with people without CHD (287). This has been supported by data from a study of older adults admitted to hospital for a MI, which reported ~10% were classified as high falls risk and ~36% were classified as a moderate falls risk (224). People admitted for a MI who were at high risk of falling had a fully adjusted hazard ratio of 3.65 (95% CI 1.67-7.99) for all-cause death within 12 months compared to people with CHD and low falls risk (224). The impact on risk of all cause hospitalisations became apparent in the moderate risk group, with the fully adjusted hazard ratio for admission within 12 months being 1.31 (95% CI 1.02-1.68), increasing to 1.64 (95% CI 1.13-2.38) for those at high risk of falling (224). The impact of falls risk on mortality and hospitalisations was largely attributed to non-cardiac causes (224) and there was a graded increase in other risk factors, such as impaired renal function, dyslipidaemia, cancer, dementia, hypertension and stroke, across the falls risk spectrum, although these were accounted for in the fully adjusted modelling (224).

The falls risk assessment marker most strongly associated with mortality and hospital admissions risk was the physical mobility Get Up and Go test (224), implying there may be a benefit to adverse outcomes from exercise training. Indeed, a meta-analysis of exercise training programs in older adults (≥65 years) found exercise training improved static and dynamic aspects of balance, fear of falling and confidence, along with decreasing the risk of falling (288). Additionally, exercise training in people with CHD has been found to

improve Up and Go Test measures and other markers of dynamic balance (223), demonstrating these benefits are available to people with CHD as well as healthy older adults. Concerningly, in people who were hospitalised for CHD and found to have a fear of falling, the rate of exercise participation (taken as a conservatively assessed three or more sessions weekly, of 30minutes or more) was 25%, which was significantly lower than the 57% rate of participation in those without a fear of falling (278). Given exercise is an important component of falls risk management (288) and a physical mobility measure was most strongly associated with mortality in people with CVD (224), increasing exercise participation in people with high falls risk is likely to improve outcomes in this population. Furthermore, exercise has been included as a strategy for managing falls risks in people with CVD at risk of falling in an American Heart Association Scientific Statement (289). Developing exercise modalities that allow people with CHD who have a fear of falling, or are at an elevated falls risk, to feel safe while they exercise may help to increase their exercise participation and reduce their risk of falling, while obtaining benefits to traditional risk factors for secondary prevention.

Musculoskeletal pain or comorbidities

The number of patients with CHD affected by musculoskeletal pain conditions varies, from 27% in a relatively young (mean age 54 years) sample of people already attending exercise-based CR (144) up to 57% in two national population based surveys (3, 137). Other studies have found prevalence rates around 50% (135, 277), indicating a significant proportion of the population with CHD have a musculoskeletal comorbidity.

People with CHD and musculoskeletal pain were less active than those without pain, with 35% of people with CHD and musculoskeletal pain reporting meeting 600 metabolic equivalent minutes per week of physical activity, while 56% of people without pain achieved this (144). In people with CVD, or at high risk of CVD, who were commencing CR, those with musculoskeletal comorbidities were significantly less likely to be meeting 30 minutes or more of aerobic exercise on five or more days per week (17% vs 28%) (277). Furthermore, musculoskeletal issues were the reason for 15% of exercise-based CR program withdrawals in women and 9% in men (279). Musculoskeletal comorbidities caused the alteration of exercise programs in 33% of people with musculoskeletal comorbidities, and those with arthritis and continuing musculoskeletal comorbidities demonstrated lower gains in aerobic capacity then those without musculoskeletal comorbidities (277). Furthermore, exercises that invoke pain or discomfort are linked to reduced adherence to exercise in people with chronic disease (284) and panels involving patients with osteoarthritis raised an issue that

pain may lead to hesitation in adopting exercise in people with arthritis (290). Encouraging exercise participation in people with CHD and comorbid arthritis is recommended not just for the cardiovascular health and secondary prevention benefits, but also for managing osteoarthritis, as per the American College of Rheumatology and Arthritis Foundation guidelines (290). Given the large proportion of patients affected by musculoskeletal pain and the impact these comorbidities have on exercise participation and outcomes, alternatives to traditional gym-based exercise are needed. Guidelines for arthritis management have indicated that low joint impact exercise alternatives may be required for these patients if traditional exercise provokes significant pain or discomfort (145, 290).

2.2.6 Summary of exercise in the management of coronary heart disease

Exercise is a core component of secondary prevention, both in international and Australian guidelines, with current guidelines including both aerobic and resistance exercise. Exercise and exercise-based CR are associated with improved survival, reduced hospitalisations, and reduced adverse cardiovascular events. Exercise benefits aerobic capacity, muscular strength, function, vascular endothelial function, body fat and lean tissue, blood pressure, lipid profiles, inflammatory markers and brain health, though further research is needed to optimise training programs to maximise these benefits. Despite the wide array of benefits from exercise training, participation in exercise-based CR and ongoing physical activity or exercise remains sub-optimal. There are many potential barriers to exercise in this population, including time pressures, lack of motivation, transport issues and clinical factors, such as a fear of falling, or musculoskeletal comorbidities. Training programs that reduce barriers to exercise for people with CHD are needed to assist with enhancing exercise participation and improving patient outcomes.

2.3 Water-based exercise

A key issue identified with traditional gym-based exercise training for people with CHD is the suboptimal adherence to exercise and ongoing physical activity, driven in part by the high proportion of people with CHD who experience barriers to exercise. A further consideration with exercise training is how to optimise vascular and cerebrovascular health. Novel exercise strategies that help to reduce barriers to exercise participation and enhance vascular function are needed to improve outcomes for patients with CHD.

The physical properties of water make water-based exercise an interesting modality to consider for people with CHD. Upright water immersion induces many physiological changes which impact the cardiovascular, renal, respiratory, nervous/autonomic and musculoskeletal systems, which in turn leads to changes in the body's haemodynamic response to exercise. This may provide an added stimulus to the vasculature, through an enhanced shear stress stimulus. Secondly, the effects on the musculoskeletal and nervous systems may help to reduce barriers to exercise in people with CHD who have musculoskeletal comorbidities or are at risk of falling. Finally, the novel environment and comfort of exercising in the water may help to provide motivation to exercise in people with CHD. This section outlines the physical properties of water immersion, the physiological changes during water immersion in healthy individuals and individuals with CHD (where evidence is available), along with the impact of water-based exercise training on health outcomes for people with CHD.

2.3.1 Physical principles of water immersion

During resting water immersion, key factors acting on the body include hydrostatic pressure, buoyancy (related to density) and temperature (291). During movement in water, viscosity creates drag resistance and turbulence (291). Water immersion impacts physiological processes in all body systems, with the profound changes in the cardiovascular system particularly relevant to people with CHD (291).

2.3.1.1 Hydrostatic pressure

Hydrostatic pressure is the force of the water pushing in on itself (292) and the body when the body is submersed in water. The equation for hydrostatic pressure (excluding the existing air pressure, adapted from Wilcock, Cronin and Hing 2006 (293)) is:

Equation 2 Hydrostatic pressure:

$$P = g\ x\rho\ x\ h$$

Where: P= hydrostatic pressure; g= gravity (9.81m.s^{-2}); ρ = water density (994 kg.m^{-3} assuming 35°C fresh water (294)); and h = height of the water column (depth) (m) (293).

The pressure exerted is depth and temperature dependant, with each 1.36cm of submersion depth associated with a 1mmHg rise in pressure (291). The pressure gradient caused by hydrostatic pressure on the upright human body works to push fluid from the

lower limbs, or submersed body parts, from the lymphatic system back into the vascular system and this increases central blood volume and fluid in the chest cavity (292). Hydrostatic pressure also exerts force on the chest wall, and submersion can lead to a cephalic displacement of the diaphragm (291).

2.3.1.2 Buoyancy

The physical law of buoyancy, often referred to as the Archimedes' Principle, states that at rest, any part of an object submerged in a fluid is acted upon by an upthrust equivalent to the weight of the displaced fluid (293, 295). The degree of buoyancy is dependent on the density of the water, which is affected by factors such as temperature, or additions of chemicals, such as salt (292). The density of fresh water at 34°C is approximately 994kg.m^3 (296), whilst the density of the average human is around 974kg.m^3, leading to a predisposition for humans to float (291). Density in humans is dependent on body composition: individuals with a higher body fat content are less dense (therefore more buoyant), requiring less effort to float (291, 293).

The buoyant force from the water reduces the weight bearing load on the lower limb joints and spine with upright immersion and the response is depth dependent (291). For example, submersion to the xiphoid process (at rest, arms out of the water) resulted in the immersed body weight being 35% of the land-based bodyweight (150). Postural changes and holding on to external supports in standing can also significantly alter the degree of weightbearing (297). This effect of buoyancy may be particularly beneficial for patients with musculoskeletal comorbidities, such as fractures, lower limb or spine injuries or pain, and arthritis, or obesity, through unloading joints and reducing the impact that occurs during exercise. This is particularly relevant to individuals with CHD, as musculoskeletal pain or arthritis has been reported by 27-57% of people with CHD (3, 135, 137, 277).

2.3.1.3 Temperature

Water temperature not only moderates the way the physical principles of water interact, it also influences many of the physiological changes elicited by water immersion. Increasing water temperature is known to reduce the density and viscosity of water (296), although these changes would be relatively small and unlikely to have significant impacts on water-based exercise therapy. However, water temperature does have a significant effect on thermoregulation during immersion. Water is an efficient conductor of thermal energy, transferring heat up to 25 times faster than air (291), and can impact the physiological effects

observed, particularly for outcomes involving blood flow and arterial function changes (298-300).

2.3.1.4 Viscosity, drag and turbulence

Viscosity occurs due to the friction between the water particles in motion and contributes to drag and turbulence (291). Drag occurs when moving a limb, or object, through the water and occurs in the opposite direction to the movement (301). The force of drag can be determined by Equation 3.

Equation 3 Drag Force:

$$F_d = c_d \frac{1}{2} \rho v^2 A$$

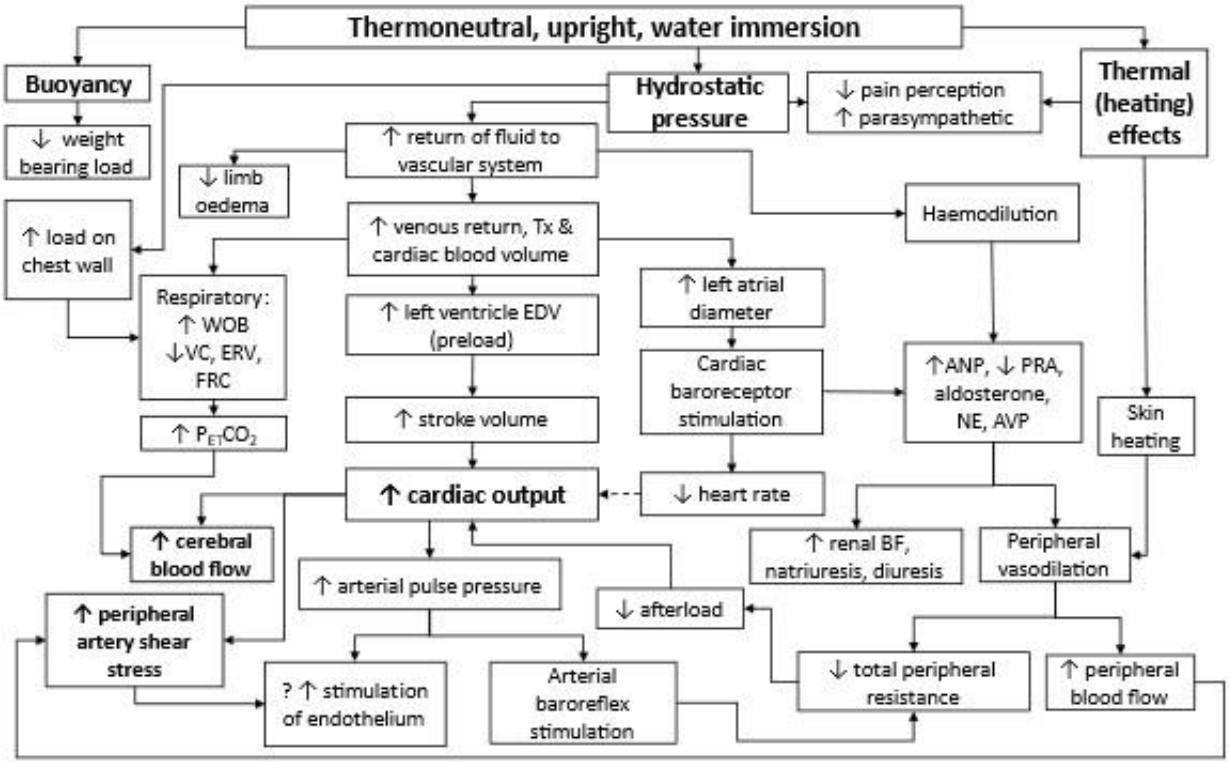
Where F_d = drag force, c_d = drag coefficient, ρ = density, v = flow velocity and A = frontal area of the body (302).

Drag is caused by the friction between the water particles and the object moving in the water (skin/surface drag) and from the turbulence created from the pressure changes around the moving object (form drag) (301). As highlighted by Equation 3, the frontal surface area plays a major role in the determination of drag, with larger surface areas creating more drag than streamlined surfaces. Knowledge of this principle can be used to make exercises harder (larger surface area) or easier (more streamlined) in the aquatic environment and is imperative to consider when designing equipment for aquatic exercise.

Turbulence occurs when there is a disturbance to laminar fluid flow and the fluid motion becomes chaotic, so that there will be a random fluctuation in velocity over time at a particular point in the fluid (303). During aquatic exercise the movement of the limbs or objects through the water creates turbulence and this can increase resistance (291). This provides a mechanism for resistance training, or concomitant aerobic and resistance training, in an aquatic environment. An example of the effects of turbulence and drag in action can be seen when greater VO_2 is needed to move the same absolute workload during water-exercise, compared to land exercise. For example, the difference in oxygen consumption when cycling at 60 revolutions per minute against a 10kg load on land was 9.7±1.7ml.kg^{-1}.min^{-1}, compared to 14.4.±3.2ml.kg^{-1}.min^{-1} for the same scenario while immersed in 32°C water (298).

2.3.2 Physiological effects of thermoneutral water immersion

The physical principles outlined above determine the physiological effects of water immersion. In healthy individuals the temperature and depth of submersion can greatly vary outcomes. This review will focus on temperatures between 30-35°C, as this is the typical range that public indoor and hydrotherapy pools are maintained within Australia. There is a close interaction between the body systems during immersion, with the cardiovascular, respiratory, musculoskeletal, renal and nervous systems being the key systems impacted, with key changes outlined in Figure 2.3.



↑: increase, ↓: decrease, Tx: thoracic, WOB: work of breathing, VC: vital capacity, ERV: expiratory reserve volume, FRC: functional residual capacity, ANP: atrial natriuretic peptides, PRA: plasma renin activity, NE: norepinephrine, AVP: arginine vasopressin, EDV: end diastolic volume, BF: blood flow solid arrow: positive relationship, dashed arrow negative relationship

Figure 2.3 The physiological effects of upright, thermoneutral water immersion.

2.3.2.1 Thermoregulation

Water immersion can alter both skin and core temperature. The impact of water temperature on the cardiovascular and other body systems will be discussed in the cardiovascular sections. This section will focus on skin and core temperature changes with resting water immersion.

The temperature at which immersion does not cause a change in core temperature has been generally attributed the term neutral or thermoneutral in the literature (304, 305).

Participant and immersion characteristics appear to play a role in determining thermoneutral water temperatures (305, 306).

Core temperature has several mediating influences, including the length of immersion time, body composition, sex and age. Immersion time was found to influence the temperature needed to prevent shivering, for example, participants immersed for one hour required water temperature to be ≥32°C to prevent uncontrolled shivering, whereas for 40 minutes water temperatures ≥30°C were sufficient to prevent shivering (304). Body composition can alter core temperature changes, with higher fat percentages associated with attenuated rate of cooling during cold water immersion (307, 308). It should be noted that only limited studies have included females in studies of thermoregulation during immersion. Whilst there are known differences in fat mass and subcutaneous fat between sexes (309), differences have been seen in the response to cold water immersion between males and females with similar fat levels (308), suggesting participant sex may influence thermoneutral range independently of body composition. Finally, ageing impacts body fat and composition (310, 311), and has been found to influence the relationship between various markers of body composition and thermoregulation in response to a non-immersed cold stress (312), suggesting ageing may impact the thermoregulatory response to warmer water immersion.

Changes in skin temperature appear to vary depending on the location of the skin, with peripheral and central skin reacting differently. Immersed peripheral skin (skin on limbs) temperature appear to follow the water temperature (304, 305, 313). Park et al. (1999) found that mean skin temperature increased from 32.4±0.35°C to 34.6±0.02°C with 34.5°C immersion and decreased to 30.1±0.03°C with 30°C water immersion (305). Ayme et al. (2014) reported similar findings in 34.2°C water, with non-immersed skin unchanged, whilst peripheral (immersed) skin increased towards water temperature (313). Contrastingly, abdominal skin (central) was significantly warmer than water temperature for temperatures below 34°C, with the difference increasing for colder temperatures (304). These temperature changes may influence factors such as skin or peripheral arterial blood flow, or sympathetic nervous system response.

2.3.2.2 Cardiovascular system

Thermoneutral water immersion elicits changes in the cardiovascular system and an overview of these changes is provided in Figure 2.3. Hydrostatic pressure acts on the submersed sections of the body, shifting fluid from the lymphatic system into the

cardiovascular system and driving the fluid centrally towards the lower pressure in the chest cavity (291, 292). This leads to increased central blood volume, with an increase of ~700ml noted for head out water immersion, which in turn increases cardiac volume (314). Simultaneously, there is a reduction in peripheral vascular resistance (291), which combines to alter cardiac function (291) in accordance with the Frank-Starling mechanism (315), discussed further in 2.3.2.2.3. These central changes in cardiac function precipitate changes in the peripheral and cerebral vessels and can trigger reflexes relating to renal and autonomic nervous system function (291, 316, 317). Cardiovascular system changes are particularly affected by variations in participant age, health status, submersion depth and water temperature (305, 306, 318, 319). Additionally, measurement techniques can affect findings, depending on whether they rely on imaging, invasive measures, or if they are based on calculations from non-invasive measures, contributing to a wide range of values reported in the literature.

2.3.2.2.1 Atrial dimensions

The literature generally agrees there is an increase in left atrial dimension of between 11-21% in healthy people with water immersion to the level of the xiphoid process (313, 318, 320, 321). There may be a step-wise increase with immersion depth, as suggested by data from Gabrielsen et al. in 2000, who observed an increase in left atrial diameter from 21% at the level of the xiphoid to 33% at the level of the neck (318), with a further study observing a significantly greater increase in left atrial diameter with neck deep immersion, compared to xiphoid level immersion in healthy people (322). The duration of immersion and activation of compensatory mechanisms can affect atrial volume findings. Increased left and right atrial size have been observed with seated immersion to the neck in 34.5°C water (+17% on resting values), however a decline in atrial volumes with prolonged immersion was noted after approximately 2 hours for the right atrium and after 90 minutes for the left atrium (321). This suggests that compensatory mechanisms occurred (321).

In people with New York Heart Association (NYHA) class II-III heart failure (mean left ventricular ejection fraction of 28%), immersion in 34.7°C water to the xiphoid process for 30 minutes increased left atrial diameter by a similar amount during immersion compared to healthy control participants (+6.1mm and +6.4mm, respectively), although the relative change was lower in people with HF due to an elevated baseline diameter (16% in HF, 27% in controls) (323).

2.3.2.2.2 Ventricular dimensions

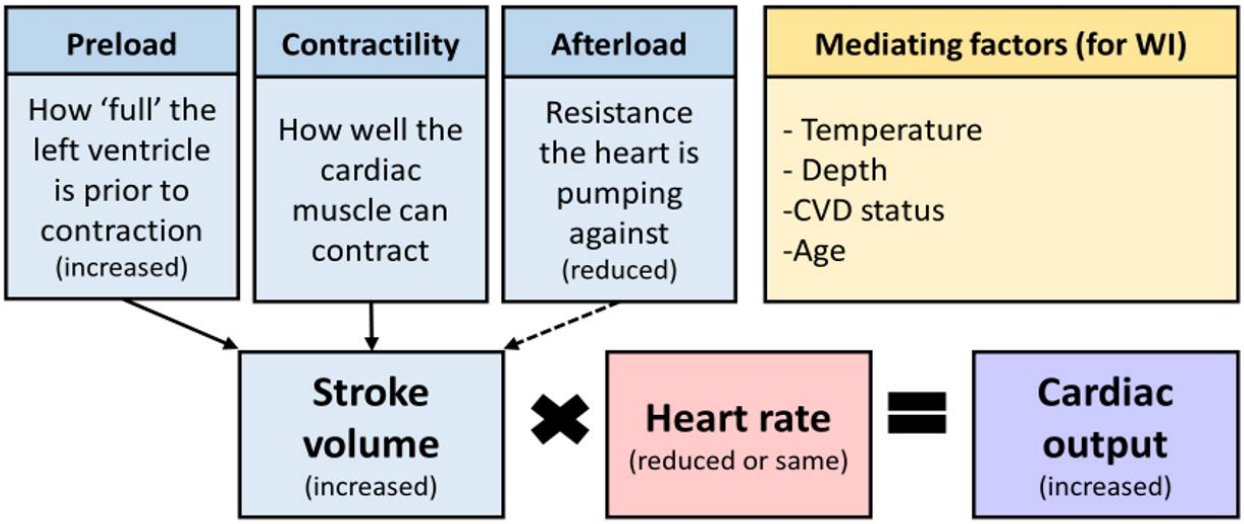
In healthy, young men, left ventricular end diastolic volume has been found to increase by 22-52% with immersion (305, 324) indicating increased preload on the heart (315). Correspondingly, small increases in left ventricular end diastolic diameter have been observed with water immersion in healthy, young males (313). Water temperature is suspected to play a mediating role in this relationship, with Park et al. (1999) finding a 35% increase in left ventricular end diastolic volume in 30°C water, but only a 22% increase in 34.5°C water (305). Park et al. also observed reduced skin temperature and increased peripheral vascular resistance at the lower water temperature, speculating that peripheral vessel vasoconstriction contributed to the difference in preload for the two different temperatures (305). Increased preload contributes to functional changes in the heart and is a component of increasing cardiac output (291).

In thirteen people with NYHA II-III chronic heart failure (CHF) immersion in 33-34°C water to the sternal notch did not further increase left ventricular end systolic or end diastolic volumes, from the distended values observed during land-based assessment. This was in contrast to significant increases in healthy control participants for both measures, however these increases occurred in the context of a lower baseline (319). While left ventricular volumes did not change from land-based measures in the people with CHF, cardiac function improved during immersion (discussed in Section 2.3.2.2.3), suggesting this level of immersion is appropriate for people with heart failure.

2.3.2.2.3 Cardiac function and related factors

Changes in the cardiac volumes, mentioned above, along with changes in peripheral vascular resistance, drive the changes in cardiac output, stroke volume and heart rate seen with water immersion (291). Cardiac output is the product of stroke volume and heart rate (315). Stroke volume is impacted by the balance of factors in the Frank-Starling mechanism, including preload, determined by the amount of ventricular filling, myocardial contractility, which is the ability of the heart muscle to contract, and the afterload, which is the resistance from the pulmonary or aortic pressure (315). This has been summarised in Figure 2.4. The impacts of water immersion on cardiac output, left ventricular ejection fraction, stroke volume, heart rate and total peripheral vascular resistance in people with and without CHD

or CHF will be described in this section. A summary of the studies involving cardiac disease is included in Table 2.1.



Solid arrow indicates an increase has a positive effect on stroke volume, dashed arrow indicates an increase has a negative effect on stroke volume, text in brackets underneath descriptor indicates the typical response during thermoneutral water immersion in healthy individuals and WI refers to water immersion.

Figure 2.4 Factors affecting cardiac output.

Cardiac output and index

With the exception of two studies (325, 326), most studies have found increases in cardiac output and cardiac index with water immersion from the depth of the xiphoid process and above in healthy, young people (305, 306, 313, 316, 318, 324, 327-333). Augmented cardiac output during immersion may assist in increasing blood flow and shear stress in the peripheral and cerebral arteries, to promote arterial health, or for patients with comorbidities such as heart failure, it may help to ensure adequate oxygen delivery during large muscle exercise to reduce fatigue (334). Whilst the finding of increased cardiac output has been consistent, the degree of increase has varied widely between studies, from 6-102% (306, 316). Studies including people with CHD and CHF also observed an increase in cardiac output or index to a varying extent (see Table 2.1), with the exception of one stepwise immersion protocol (gradual water entry over 12 minutes) (335). Potential factors contributing to this variation between studies may be assessment technique, participant position, water depth and temperature, and participant factors, such as age.

Table 2.1 The effects of acute water immersion in people with coronary heart disease or chronic heart failure.

Study	Settings	Condition	HR	SV/ SV index	CO/CI	SBP/ [MAP]	DBP	SVR/TPR
Cider (2006)(319)	33-34°C Sternal N	CHF II-III	-15%*	+37%*	+14%	[0%]	-	
Grüner Sveälv (2009)(336)	34°C Sternal N	CHF II-III	-10%*	+47%*	+35%*	[-7%]*	-	-29%*
Shah (2019)(337)	33-35°C Supine	CHF I-II	-	+26%*	+30%*	-	-	-33%*
Schmid (2009)(338)	32° Chest	CHD	-13%*	-	+14.5%	-8%	-	↓from pelvis*
Schmid (2009)(338)	32° Chest	CHF	-14%*	-	+17.3%*	-5%	-	↓from chest*
Schmid (2007)(339)	32° Chest	CHD	-11%?	+41%?	+21%?	-2%?	-17%?	-30%?
Schmid (2007)(339)	32° Chest	CHF	-7%?	+17%*	+16%*	-3%?	-18%?	-21%?
Gabrielsen (2000)(323)	34.7°C Xiphoid	CHF II-III	-6%*	~+40%*	+37%*	+5%*	+4%	~-20%*
Schega (2007)(335)	U°C Shoulders	CHD stepwise	↓	↓*	↓*	=	↓*	-
Schega (2007)(335)	U°C Shoulders	CHD immediate	=	↑*	↑*	↓*	=	-
Meyer (2004)(340)	32°C Neck	Moderate CHF	-	M+41%* S=	-	-	-	-
Mourot (2010)(341)	30-32°C 1.3m	CHD (untrained)	+10%?	+33%?	+20%?	+6%? [-2%]?	-8%?	+21%?
Mourot (2010)(341)	30-32°C 1.3m	CHD (trained)	-6%?	+30%?	+14%?	+4%? [-4%]?	-11%?	-15%
Mourot (2010)(341)	30-32°C 1.3m	CHF (untrained)	-2%?	+13%?	+7%?	-1%? [-2%]?	-4%?	-8%
Mourot (2010)(341)	30-32°C 1.3m	CHF (trained)	-	+22%?	+15%?	1%? [-4%]?	-8%?	-9%

Data displayed are the percentage changes from dry conditions/ baseline measures, or the directional change from dry conditions. HR = heart rate, SV = stroke volume, CO = cardiac output, CI = cardiac index, SBP = systolic blood pressure, [MAP] = mean arterial pressure (scores delineated by square brackets), DBP = diastolic blood pressure, SVR = systemic vascular resistance, TPR = total peripheral resistance, ↓ = reduced, ↑ = increased, U°C= unspecified temperature, Sternal N = sternal notch, CHD= coronary heart disease, CHF= chronic heart failure, I-II = New York Heart Association stage 1 to 2, II-III = New York Heart Association stage 2 to 3, stepwise = gradual water immersion (4 stages over 12 min), immediate = immersion straight to shoulder depth, M = moderate, S = severe, ?= p not specified, ~ = approximate measure derived from graph, = = no change from baseline,*= $p<0.05$.

Assessment method

The clinically accepted ‘practical’ gold-standard for cardiac output assessment is pulmonary artery catheterisation with thermodilution, which is invasive, not without error (342) and would be difficult to perform during water-based assessment. Accordingly, alternative less or non-invasive methods have been developed, although there is no consensus on the best alternative methodology (342, 343). Consequently, cardiac output assessment methods vary between studies, with techniques including echocardiography (313), gas rebreathing (318, 327), impedance cardiography (305) and photoplethysmography (316), making comparisons between studies challenging and potentially altering the results.

Participant position

Participant positioning ranged widely between studies, including sitting semi-reclined on chairs (313), semi-recumbent supported standing (325), sitting stationary on a bike (306) and standing (316). This makes between-study comparison difficult, as cardiac output is significantly affected by body position (344).

Immersion depth

Immersion depth appears to impact cardiac output, with studies that have encompassed a range of depths finding graded increases in cardiac output with increasing depth (318, 327).

Water temperature

To date water temperature has not been found to play a substantial role in cardiac output differences for temperatures close to swimming pool ranges (in the range of 25-36°C). Only small, non-significant, differences have been seen between cooler and warmer immersions at the same depth level for the iliac crests (345), sternal angle (330) and neck (305).

Participant characteristics

Participant factors have been found to impact cardiac output or index outcomes. Younger, female participants (mean age 22 years) were found to have significantly greater changes in cardiac index at the same immersion depth and temperature when compared to older females (mean age 54 years) with a 102% increase in younger females and a 49% increase in older females (306). Meanwhile Derion et al. (1992) found the 23% increase in

cardiac output in young males (20-29 years) was not statistically different to the 9% increase seen in middle-aged males (40-54 years) (328). Of note is that the majority of participants across studies have been young males, with limited numbers of female and older participants, so the applicability of these findings to all healthy populations may not be appropriate, especially given the recent acknowledgement of sex differences in cardiovascular physiology and the development of pathology (346). Additionally, health can impact cardiac output findings, for example in people with CHF the increase in cardiac output with water immersion was not significant (14%), whilst in healthy participants under the same conditions the 31% increase reached significance (319).

Left ventricular ejection fraction

In people with CHF (NYHA II-III), left ventricular ejection fraction has been observed to increase during 33-34°C water immersion to the sternal notch, from 31% to 35% (336) and from 24% to 27% (319), while in healthy control participants ejection fraction was not significantly altered (55% to 59%) (319).

Stroke volume

Similar to the increases in cardiac output with water immersion, stroke volume and stroke index have tended to increase in most (305, 306, 313, 316, 318, 324, 327, 328, 330-333, 347), but not all (321, 326) studies in healthy individuals. Again, there was substantial variation in the absolute and relative changes reported by studies, for the same methodological reasons mentioned above for cardiac output/index. Similar to findings in cardiac output, increasing water depth was associated with increased stroke volume (318, 327). Like cardiac output, no significant effects of temperature were seen on stroke volume in studies of one hour or less (305, 330, 347). Age was found to significantly lessen the observed increase in stroke index in females, from +95 % in younger females (mean age 22 years) to +56% in middle-aged females (mean age 54 years) (306), and while a similar trend has been seen in stroke volume values between middle aged and younger males (+12% in 40-54year old males, and + 34% in 20-29 year old males) this did not reach significance (328).

In people with CHF (NYHA class II-III), seated immersion in 34.5-35°C water to the fourth rib resulted in a significant increase in stroke index (+41%), however this was less than the healthy control group (+58%) (348). Other studies in people with CHF and CHD have found stroke volume or index increase between 17-47% (319, 335-337, 339), see Table 2.1. One study of step-wise immersion did not find an increase in stroke volume in

people with CHD, although the same cohort responded with a stroke volume increase when rapidly entering the water (335). In this study there were three separate sub-groups in the cohort based on echocardiographic features, and although the study was underpowered to analyse these groups, the divergence of the responses between these groups may have affected the conclusions of step-wise versus immediate immersion (335), suggesting caution when interpreting this study. Stroke volume is one of the components for calculating cardiac output and the majority of findings support stroke volume changes being the likely mechanism for this increase, particularly given the heart rate changes discussed below.

Heart rate

Heart rate is a key contributing factor in the calculation of cardiac output (see Figure 2.4). However, the physiological effects of water immersion on heart rate have been less consistent, with some studies in healthy people finding little to no change and others finding substantial variation. Seven of the sixteen cohorts examined exposed to 34-34.9°C water immersion reviewed observed less than a 5% change from baseline values (305, 306, 313, 324, 329, 331, 349), four cohorts demonstrated a 5-10% reduction in heart rate (306, 329, 333, 350), and five cohorts demonstrated a reduction greater than 10% (318, 320, 326, 330, 347). Immersion in temperatures between 25-32°C reduced heart rate by between 7-32% (305, 316, 325, 330, 347, 351). The reduction in heart rate has been associated with the increased cardiac volume and is thought to be reflexive (315, 352, 353). Further outside of the thermoneutral range, heart rate increases during cold (14°C) (354) and hot (39°C) (355) water immersion. Colder water immersion at rest can lead to shivering and increased oxygen consumption (354). Hot water immersion likely increases heart rate to maintain the increased cardiac output required to cope with the increase in cutaneous vasodilation and skin blood flow for thermoregulation (356).

Depth alters the heart rate response to immersion. In healthy individuals during 29-30°C immersion heart rate is unchanged from standing heart rate during ankle or knee immersion, and becomes significantly reduced from the hip, reduces further to the umbilicus and then remains relatively unchanged between the xiphoid, shoulder and neck levels (353). Other studies in healthy, young people in thermoneutral water support the findings of minimal impact to heart rate between the xiphoid and neck (318), and navel, xiphoid and neck (326), while significant differences were observed between hip and neck immersion (357). Fahri et al. who conducted a graded immersion study in healthy males aged 25-34 years in 35°C water and found that at the level of the hip, heart rate was 4% lower than dry values, with further immersion to the depth of the xiphoid, the heart rate showed an 11%

reduction on dry values, however when submersed to the chin heart rate was only 7% lower than dry values, although the increase in heart rate with neck immersion was not seen in most participants, with most plateauing from xiphoid values (358).

The depth-dependent effect is tempered depending on resting standing heart rate. For xiphoid depth immersion the relative reduction from standing heart rate was -1 beat per minute in those with a standing resting heart rate between 50-59 beats per minute, -5 beats per minute in those with a standing resting heart rate between 60-69 beats per minute, up to -34 beats per minute in those with a standing resting heart rate between 120-129 beats per minute (353). The depth-dependent impact of thermoneutral immersion (34-35°C) in people with CHD and on beta-blockers or other vasoactive medications is unknown and requires investigation.

The impact of ageing on heart rate response patterns in healthy people during water immersion remains unclear. Kruel et al. (2014) found no impact of age on heart rate response patterns (353), whilst Itoh et al. (2007) found a blunting of heart rate changes to water immersion in older (mean age 68 years), compared to younger (mean age 20 years) people (326). The participants in the Kruel et al. study were all regular water exercisers for at least 12 months prior to study entry and the older adult cohort was mostly female (88%) (353), while in the study by Itoh et al. the older adult cohort included people with comorbidities (27% were treated for hypertension with diuretics) and the sample was exclusively male (326), which may have impacted this difference.

The effects of acute water immersion on heart rate in people with CVD is outlined in Table 2.1. The reduction in heart rate was similar between healthy younger males (mean age 33 years) and males with CHD (mean age 57 years, on beta blocker medication) reducing by 10% and 11%, respectively (339). Temperature was found to influence heart rate in people with CHD, with heart rates reducing during 29-32°C water immersion to the chest (338, 359). while no changes occurred in cool water (22°C) immersion (338). These changes suggest heart rate is similarly impacted by water immersion in people with CHD. Reduced heart rate during water immersion likely contributes to stroke volume and cardiac output increases (315) and if the changes in heart rate persist with exercise, this could alter exercise prescription.

Peripheral resistance

Total peripheral vascular resistance (TPR) or systemic vascular resistance (SVR) have generally been found to reduce with water immersion in temperatures above 30°C

(305, 313, 322, 324, 329, 331, 333). Cooler water temperatures were associated with an attenuated reduction (305), or an increase in TPR (325) compared to the same immersion positions in thermoneutral or warm water, likely due to peripheral vasoconstriction in cold temperatures. Reductions in TPR/ SVR reduces afterload on the heart, and can lead to increases in cardiac output (315).

Different vascular beds contribute to peripheral resistance. In thermoneutral water measurements using ^{133}Xenon washout, subcutaneous forearm vascular resistance was reduced during both xiphoid and neck level immersion, whilst only neck level immersion significantly reduced forearm skeletal muscle vascular resistance (322). In people with CHD or CHF reductions in TPR of ~20-30% have been observed (323, 336, 339) (Table 2.1), indicating participants with CHD or CHF likely still obtain benefits to afterload.

2.3.2.2.4 Blood pressure

The effects of water immersion on blood pressure have been varied in the literature, with temperature playing a mediating role. Thermoneutral water immersion (between 34.0-34.9°C) demonstrated changes of less than 10% in mean arterial pressure (MAP), with the difference from land measures only significant in half of the 10 cohorts in studies examined conducted at the level of the xiphoid or deeper (305, 306, 313, 318, 320, 329, 349).

In healthy individuals, temperature can impact blood pressure responses. During thermoneutral (34.5°C) water immersion to the neck, SBP increased by 8% but DBP was unchanged, while immersion in cooler water (30°C) increased SBP similarly to thermoneutral immersion, although DBP increased approximately 15% (significantly different from thermoneutral immersion) (305). During 30°C immersion, skin and oesophageal temperatures significantly reduced (305), and cold stimuli are known to elicit cutaneous vasoconstriction (360). Indeed, during 30°C immersion to the level of the right atrium in healthy, young participants, forearm and chest cutaneous vascular conductance were reduced (361) which may indicate that cutaneous or peripheral vasoconstriction may be related to the rise in blood pressure seen at this temperature. This is an important consideration for selecting water temperature in people with CHD, as hypertension (a common comorbidity of CHD (133, 134)), is associated with an exaggerated vascular constrictor response to cold stressors (360).

The effect of ageing on blood pressure responses during water immersion has been variable. Ueno et al. (2005) found significant increases in SBP with older males (mean age

59 years) and no significant changes in younger males (mean age 24 years), during immersion to heart level (362), with the difference in part thought to be due to differences in carotid compliance and baroreflex sensitivity with ageing (362). However, a study in younger (22 years) and older (55 years) females found that head out water immersion in 34.5°C significantly increased SBP in younger females, and both groups increased mean arterial blood pressure. Whether these observations are due to sex or ageing is unknown.

In people with CHD or CHF the effects of water immersion on blood pressure are varied, from a small (5%) increase in people with CHF evaluated for cardiac transplant (323) through to large (~17%-18%) DBP reductions in people with stable CHF and CHD (339) (see Table 2.1). This may be partially due to differences in vascular thermoregulation in hypertensive conditions (360), and some evidence suggests that while central responses to increased cardiac volume is preserved in people with CHF, subcutaneous vascular responses are impaired (323), as such there may be a gradient of impairment with varied clinical presentations.

Pulse pressure

Changes in pulse pressure (the difference between SBP and DBP) with immersion have been found to vary between studies. Some studies found no change in radial or brachial artery pulse pressure in 34-35°C water, submerged to the depth of the xiphoid or mid-chest in seated or semi-recumbent positions (313, 331). These studies used non-invasive measures of arterial pressure. Contrasting this, significant increases in pulse pressure have been observed in other studies at the same temperature (34-35°C), with immersion levels between the xiphoid and neck (318, 320, 329, 333, 357), with Gabrielsen et al. (2000) including invasively measured brachial artery blood pressures (318). Ageing may impact the pulse pressure response, with Ueno et al. (2005) finding a significant 28% increase in pulse pressure with mid chest immersion in older (mean age 59 years) participants, whilst there was only a tendency to increase in younger (mean age 24 years) participants (+10%) which was not significant (362).

Increased pulse pressure can increase circumferential stress (strain) on arteries, which may enhance the expression of endothelial nitric oxide synthase (eNOS) and other endothelium-dependent vasodilator pathways, although this stress can also elicit increases in reactive oxygen species and can encourage atherogenesis with chronic exposure (e.g. chronic hypertension) (232). Short duration increases in pulse pressure, such as during water immersion or exercise, may have positive effects on the artery from the enhanced

eNOS expression (232), however further research is needed to clarify the short-term effects of increased cyclic strain on arteries.

In people with CHD, 30-32°C water immersion (1.3m depth) increased pulse pressure by 28% in people with CHD and 5% in people with CHF (341) before a training program and 29% and 15% for CHD and CHF respectively, after the program. During 32°C water immersion to the chest, the calculated change in pulse pressure (using SBP and DBP data) was +6% for healthy control men, +26% for males with CHD and +24% for males with CHF (339). Meanwhile in 33-34°C water immersion to the sternal notch, the change in pulse pressure was ~+10% in people with CHF (mean age 72 years), while in healthy control participants (mean age 72 years) the pulse pressure was ~+22% (calculated from SBP and DBP changes from land to immersion) (319).

Differences between studies may be due to a range of factors, for example in Schmid et al. (2007) the baseline SBP (a determinant of pulse pressure) was 122mmHg in healthy individuals and 113mmHg in people with CHF (339). Training status and CVD type have also influenced pulse pressure (341). Additionally, there may be effects from the different water temperatures used between the studies. Despite the differences between cohorts, pulse pressure increased between 5-30% in people with CVD, indicating this modality may be useful for improving vascular function.

2.3.2.2.5 Arterial function and health

The impact of acute thermoneutral water immersion on peripheral arteries has not been well described in the literature. In healthy individuals, acute thermoneutral water immersion led to increases in arterial compliance (331) and forearm skeletal muscle blood flow (322), which may indicate an increased shear stress stimulus on the vascular endothelium. Increased shear stress stimulates the vascular endothelium to release vasoactive substances and leads to smooth muscle relaxation and vasodilation (13, 232). Indeed, after more than 30 minutes of 34.2°C water immersion to the xiphoid process, brachial artery diameter and blood flow significantly increased, although shear stress was unaltered at this timepoint (313). The shear stress stimulus may have been greater during the initial phase of immersion, as the peak cardiac volume change during immersion occurs at around 6 seconds (363), and vasodilation is known to occur within minutes of an increase in shear stress (227), highlighting the rapid response of the cardiovascular system to water immersion. An initial increase in shear stress may have led to the observed brachial artery dilation observed at the 30 minute time point (313). An increase in diameter is associated

with a subsequent reduction in shear stress on the arterial wall, in accordance with Poiseuille's law (364), which may explain the lack of change in shear stress at the 30 minute time point.

Potential mechanisms for the increase in arm blood flow seen with immersion include the impact of hydrostatic pressure during water immersion increasing central blood volume and cardiac output (see section 2.3.1.1 on hydrostatic pressure, Section 2.3.2.2 for cardiac volumes and function), the thermal effects leading to increased peripheral blood flow and cutaneous vasodilation for thermoregulation (236) or a combination of these effects. In addition to these blood flow changes, a reduction in sympathetic neural activity has been observed during thermoneutral immersion (317, 322) which may facilitate reductions in peripheral vasoconstriction (365).

The acute shear stress response to thermoneutral water immersion and impact of this on shear stress responses during exercise in people with CHD has not been established. If there is an additional shear stress response from resting immersion in thermoneutral water in people with CHD, and this is sufficient to obtain the same benefits to vascular endothelial function as exercise, or local and global body heating seen in healthy people with repeated exposure (236, 366), then repeated thermoneutral water-immersion may become a tolerable option for obtaining vascular health benefits in severely deconditioned patients. Alternatively, if these changes are additive to those seen with exercise there may be a greater stimulus on the endothelium with water-based exercise training.

The effects of 34.5°C water immersion on arterial compliance was examined by Boussuges (2006), who found immersion to the mid-chest in a seated position increased large (C1: aorta and main branches) and small (C2: distal circulation) artery compliance in healthy young males and females (331). In people with CHD, water immersion in 30-32°C to a depth of 1.3m did not significantly change arterial compliance, however there was substantial variability (341), requiring caution when interpreting these findings. Poor peripheral artery compliance has been associated with an increased risk of coronary stenoses (367), highlighting the importance of this for patients with CHD.

Temperature appears to be a mediator for the vascular effects of water immersion. In cool water (30°C) an increase in sympathetic activation may occur, as significant increases in skin sympathetic nerve activity have been seen with skin temperatures below 32°C (368), and during 30°C resting water immersion skin temperature has been found to

reduce in the immersed periphery (304, 305). Furthermore, reductions in skin cutaneous vascular conductance have been observed during 30°C immersion (361), and cold stress to a large portion of the body can lead to reflex peripheral vasoconstriction (360). Additionally, 30°C immersion led to reductions in brachial artery blood flow, conductance and antegrade shear stress alongside an increase in retrograde shear stress (299). The contrast between the 30°C data and the thermoneutral studies highlights the importance of temperature in peripheral vascular regulation during immersion. Reassessing brachial artery diameter and flow patterns at different water temperatures and during exercise would assist in determining the mechanism behind the flow and diameter changes and address the disparate results reported between papers.

2.3.2.2.6 Cerebrovascular

Water immersion has been found to influence the function of the cerebral circulation (316, 361, 369). Transcranial Doppler ultrasound (TCD) (316, 361) and functional near-infrared spectroscopy (369) have been utilised to measure markers of cerebral blood flow and cerebral oxygenation. These changes appear to result from multiple mechanisms and occurred both with (316) and without (369) central haemodynamic changes.

Middle and posterior cerebral artery velocity (MCAv and PCAv, respectively), are often used as surrogate measures of cerebral blood flow. Both MCAv and PCAv increased during 30°C water immersion to the level of the right atrium in young, healthy participants (316, 361). Carter et al. (2014) found 8.5% and 7.3% increases in MCAv and PCAv respectively (316), with Pugh et al. (2015) reflecting similar changes (361). More recently, 32°C water immersion to the waist was found to significantly increase MCAv in healthy, young people compared to land-based measures, while 38°C water immersion did not (300). Worley et al. (2021) produced similar results for MCAv between 35°C (+4-8%) and 39°C (-2-3%) during immersion to the sternal notch (355).

The possible mechanisms resulting in this resting increase in CBF include increased cardiac output, increased MAP, and increased end tidal carbon dioxide ($P_{ET}CO_2$) (increased levels of arterial CO_2 lead to increases in cerebral blood flow (370)). Indeed, moderate and strong correlations have been observed between changes in MCAv and changes in MAP and $P_{ET}CO_2$, respectively during immersion (316). However, while $P_{ET}CO_2$ was strongly correlated with MCAv, significant increases in MCAv have been observed during immersion to the hip (316) and waist (300) without a significant change in $P_{ET}CO_2$. Furthermore, significant differences were seen in MCAv with water immersion between 32°C and 38°C,

despite similar levels of $P_{ET}CO_2$ (300), suggesting other factors contribute to increasing cerebral blood velocity with water immersion, particularly during heat stress (300). Contributing to the investigation of the effects of increased $P_{ET}CO_2$ during water immersion, Sackett et al. (2018) investigated the impact of one hour of seated 35°C water immersion to the neck, compared to a dry seated control condition with, added CO_2 to match the $P_{ET}CO_2$ increase observed during water immersion (371). MCAv was elevated with water immersion compared to both the baseline assessment, and the dry time-control condition with matched $P_{ET}CO_2$, which did not exhibit any change in MCAv (371). This highlights that increased $P_{ET}CO_2$ is not the sole driver of increased cerebral blood velocity during water immersion. The haemodynamic changes during water immersion were akin to other studies, with an increase in cardiac output and stroke volume, transient reduction in mean arterial pressure, a reduction in total peripheral resistance and no change in heart rate (371). With the exception of an increase in mean arterial pressure over time, these variables were unchanged in the dry condition (371). These differences in haemodynamic variables between the dry and water-immersed conditions, despite similar $P_{ET}CO_2$ changes, indicate the systemic haemodynamic changes associated with water immersion likely play a role in the changes seen in the cerebral circulation during water immersion.

Another perspective on the potential mechanisms of increased cerebral blood flow during water immersion was provided by a study using functional near infrared spectroscopy in 34°C water (369). Participants were seated in a tank for five minutes, then the tank was filled over five minutes until the participants were immersed so the anterior aspect of the thigh was just underwater and remained at this depth for five minutes (369). Oxygenated haemoglobin was significantly increased during the immersion period in the primary somatosensory area, the parietal association area, and then later the primary and supplementary motor areas of the brain (369). It is unlikely these changes were driven by increased $P_{ET}CO_2$, as a previous study did not find any increases in $P_{ET}CO_2$ with hip level immersion (316). Moreover, the increase occurred in the absence of blood pressure or heart rate changes (369), indicating a change in cerebral metabolism driven by the changes in sensory input, rather than a MAP/ $P_{ET}CO_2$ driven response, however cardiac output was not assessed. Limitations of this study included the lack of cardiac output assessment, that the seated control and immersion order wasn't randomised, and that participants were seated, rather than standing, so the full effect of hydrostatic pressure is unlikely to have been utilised (as it is a depth dependent response). Furthermore, participants could become distracted, or fidget after the prolonged period of sitting, which could alter cerebral metabolism. One of the limitations of functional near infrared spectroscopy is that it can pick up changes in skin

blood flow (372), however this study measured skin blood flow and found no changes, suggesting the changes were due to alterations in the cerebral circulation.

In combination, these studies show that water immersion can increase cerebral blood flow and may increase cortical activation/ cerebral metabolism, potentially through a variety of mechanisms, in young, healthy individuals. The effects of acute water immersion and water-based exercise on cerebral blood flow in people with CHD is unknown. The impact of water-based exercise on cerebral blood flow will be discussed further in Section 2.3.3.2.4.

2.3.2.3 Respiratory system

Hydrostatic pressure is one of the driving forces of respiratory changes with water immersion. Increased venous return leads to increased thoracic blood volume (291) and, depending on the depth of immersion, there can be mechanical effects on the abdomen (373) and chest wall (374). The effects on the respiratory system appear to be depth and posture dependent (327, 373-375). Most of the included studies had small sample sizes and were conducted in younger, healthy males.(316, 327, 376-379). More data are required to determine the effects in older people, females and people with comorbidities.

The greatest changes to lung volumes occur with submersion between the xiphoid and the base of the neck (374, 375). Increased thoracic blood volume with neck deep, steady state immersion was responsible for nearly 60% of the reduction in vital capacity seen with in a small sample of healthy males (379). Additionally, higher airway impedance/resistance was recently found by Hoshi et al. (2022) with immersion above the level of the xiphoid process, with increased pulmonary blood volume thought to be a contributing factor (376). This increase in intrapulmonary blood volume increases the stiffness of the lungs and increases the work of breathing (351, 375). In light of this, ensuring water-immersion is at an appropriate (lower) depth for people with respiratory comorbidities, muscle fatigue, or pulmonary vascular congestion, will assist in managing the added work of breathing and potential pulmonary congestion. with water immersion and immersed exercise.

In addition to increased pulmonary blood volume increasing lung stiffness, hydrostatic pressure acting on the thorax adds resistance to thoracic expansion, further increasing the work of breathing. During immersion to the base of the neck 25-27cmH_2O of positive pressure breathing was required to return expiratory reserve volume to dry land values (375). Water immersion to the clavicles has been found to reduce maximum inspiratory

pressure (374), while shallower immersion to the xiphoid is associated with less impact on the respiratory system, with one quarter of the change in expiratory reserve volume occurring at the xiphoid level (375). The added hydrostatic pressure and workload means the depth of immersion needs to be picked carefully for people with inspiratory muscle weakness to ensure they are not overburdened, and inspiratory muscle weakness is common in people with CHD (380). Alternatively, future research could investigate the potential of graded water immersion as a training load for improving inspiratory muscle strength. Water-based exercise training has been found to significantly increase inspiratory muscle strength in people with chronic obstructive pulmonary disease compared to a control group, while land-based exercise training did not (381). Furthermore, in healthy, young males, performing treadmill exercise while immersed to the level of the 4th rib induced significantly greater inspiratory muscle fatigue than matched intensity (60% of VO_{2peak}) land-based exercise (382). These studies suggest further research into water-based exercise for improving inspiratory muscle strength is indicated for the sub-population of people with CHD and inspiratory muscle weakness, particularly as increasing inspiratory muscle strength in people with CVD and inspiratory muscle weakness can improve exercise training outcomes (380).

2.3.2.4 Musculoskeletal system and pain responses

Warm water immersion impacts the musculoskeletal system through the supportive effects of buoyancy and can have thermal effects reducing pain perception (291). Buoyancy helps to support the body in the water and relieves the weightbearing load on lower limb joints and the spine (150, 291). The reduction in weightbearing is depth and sex specific, likely related to differences in body composition (383). For example, immersion to the xiphoid was related to 35% (range 30-37%) weightbearing in males and 28% (range:25-31%) in females, with immersion to the 7th cervical vertebrae associated with 8% weight bearing in both sexes (383). These reductions in weight bearing load may assist participants who have conditions such as arthritis, lower limb or spinal pain to exercise more comfortably, as there are less compressive and shear joint forces affecting the lower limb and spinal joints (150). Additionally, partial weightbearing may be necessary during injury or joint replacement recovery (384), with water-based exercise allowing easier mobility to retrain activities and complete rehabilitative exercise. The ability to reduce weight bearing load while allowing exercise and movement is particularly relevant for people with CHD, due to the high proportion of people reporting comorbid arthritis or joint pain (3, 135, 137) which can act as a barrier to exercise in this population (137, 181).

In addition to reducing joint loading, pain perception may be attenuated during thermoneutral water immersion. Murine models of acute immersion have found warm (35°C), but not cool (25°C), water immersion reduced mechanical pain response, acting at both spinal and peripheral levels, in a persistent inflammatory pain model (385, 386). Chronic inflammatory pain has been identified in both osteo- and rheumatoid arthritis (386). These studies suggest warmer water immersion may be beneficial for people with musculoskeletal comorbidities if the pain results translate to humans. Reducing pain during water immersion may be beneficial for increasing exercise participation in people with CHD and musculoskeletal comorbidities, as the absence of negative experiences (like pain) has been identified as a key factor for increasing adherence to physical activity in adults with chronic disease (284). This will be discussed in greater detail in Section 2.3.3.2.5.

2.3.2.5 Nervous system

2.3.2.5.1 Central nervous system, postural control and cognition

Along with the changes in cerebral blood flow and perfusion (see Section 2.3.2.2.6), changes have been seen in cortical activation (369) and cognition (387) during water immersion. Thermoneutral 34°C water immersion to the femur level in sitting in young males (mean age 22 years) increased oxygenated haemoglobin concentrations in the primary somatosensory and parietal association areas of the brain, followed by later increases in the primary and supplementary motor areas. These observations were made in the absence of changes in systemic haemodynamic or skin blood flow (369), suggesting the changes may result from increased cortical activation. These changes may reflect the multi-sensory stimulus on the immersed limbs, with the water providing tactile, pressure and thermal input. Whether the competing sensory stimuli play a role in pain inhibition or skill acquisition remains to be determined.

Some cognitive tasks were found to be favourably influenced by chest deep water immersion in young people (mean age 23-24 years), with word recall improving by 7% and listening errors decreasing by 42% and 45% for single and dual tasking, compared to non-immersed conditions (388). In older adults (mean age 72 years) water immersion also had a positive effect on listening errors in a cognitive auditory vigilance assessment (387).

Postural control may be influenced by water immersion. The centre of pressure area (a measure of postural sway) was up to 164% larger during immersion in chest deep water in young, healthy individuals (mean age 24 years) (388), and 136-159% greater in older

adults (mean age 72 years) (387), suggesting postural control is more difficult in the water than on land. This may be related to buoyancy effects shifting the centre of gravity upwards. These findings indicate that water may be a good environment for training balance tasks, by providing both a safe environment for practice, and through adding challenges to postural control. This is particularly relevant to people with CHD who are at an increased risk of falling (287).

2.3.2.5.2 Autonomic nervous system

Thermoneutral water immersion has been associated with a reduction in sympathetic nervous system (SNS) activity and an increase in parasympathetic nervous system (PNS) activity (389), although these effects may be attenuated with ageing (317, 326). Increased PNS and reduced SNS activity has been suggested to reduce the risk of cardiac events and arrhythmias (389). The main methods used in the literature for assessing autonomic nervous system function with water-based exercise are muscle sympathetic nerve activity (MSNA), skin conductance and heart rate variability (HRV).

Muscle sympathetic nerve activity

Muscle sympathetic nerve activity induces vasoconstriction in the vascular smooth muscle (390). Mano et al. (1991) assessed MSNA in healthy adults, ranging from 18-62 years with graded immersion up to the neck in 34°C water (317). Greater reductions in MSNA were seen with increasing depth and this was associated with reductions in leg volume and total peripheral resistance, and increases in stroke volume (317).

Skin conductance and sympathetic nerve activity

Reduced skin sympathetic nerve activity has been observed with water immersion (317, 391). Mano et al. (1991) employed microneurography to show that skin sympathetic activity was attenuated during water immersion, but this attenuation was less than that seen for MSNA (317). Sato et al. (2017) observed that water immersion in 34°C water blunted the increase in skin sympathetic activity seen in response to cognitive stress (391). While increased skin sympathetic activity in response to the cognitive stress was considered to support the increase in executive function required to complete the task, the attenuation was not associated with any reduction in task performance (391). This suggests water immersion may have beneficial sympathetic nervous system effects without impairing executive function.

Heart rate variability

Heart rate variability provides an indicator of neurocardiac function, providing information on autonomic nervous system dynamics (359) and was found to be impaired in people with CHD compared to control participants (392). Reduced HRV in CHD patients is associated with increased mortality (393). There are three main methods of analysing HRV, time-domain (measures relating to normal to normal R wave intervals), frequency domain (spectral analysis) and non-linear metrics (394). Spectral analysis has been more commonly used in the water-immersion literature during short term (5 minute) recordings, and provides values for very low frequency (≤0.04Hz), low frequency (0.04-0.15Hz), and high frequency (0.15-0.4Hz) components of HRV (395).

In healthy, young participants, thermoneutral water immersion between 34-35°C was found to shift the frequency spectra towards a favourable reduction in the low to high frequency ratio (associated with parasympathetic dominance) (391, 396).

Dionne et al. (2018) investigated the impact of supine positioning, standing on land and standing in 29°C water immersed to the xiphoid in people with CHD or stable CHF on short-term HRV (359). Compared to standing on land, water immersion reduced heart rate and low frequency normalised units, and increased markers of beat-to-beat variability and high frequency normalised units. When compared to supine positioning (which is known to increase cardiac output (397) and pressures (340)) only markers of beat-to-beat variability remained increased (359). If these acute effects translate into training outcomes this would be an important finding for people with CHD, as increasing HRV is associated with better outcomes and survival (393, 398).

Summary

Cardiac disease is associated with increased sympathetic dominance, due to maladaptive chronic changes after myocardial ischaemia (399). This can predispose the individual to further cardiac dysfunction, inflammation and arrhythmia (399), and PNS and SNS imbalance is associated with adverse outcomes and death (389, 400). Water immersion shifts the autonomic nervous system balance towards parasympathetic dominance, through reducing SNS activity in healthy people (317, 389), with preliminary findings of positive autonomic nervous system changes in people with CVD (323, 359). Whether these positive effects are further augmented in response to water-based exercise training in people with CHD remains to be investigated.

2.3.3 Physiological effects of acute water-based exercise in people with and without cardiovascular disease

2.3.3.1 Thermoregulation during exercise

While thermoneutral temperatures during resting water immersion are generally between 34-35°C (see section 2.3.2.1), the temperature required to maintain thermoneutrality is reduced during water-based exercise, dependent on exercise intensity (401) and immersion depth (300, 402).

During immersion to the neck, low-to-moderate intensity exercise in temperatures ≤25°C reduced or prevented increases in core temperature during exercise (401, 403). Higher intensity exercise only failed to increase core temperature in water immersion ≤24°C (401). Craig and Dvorak (1968) observed that in males with a resting VO_2 of 0.28L.min^{-1}, rectal temperatures initially decreased from the onset of immersion for all water temperatures, and for low intensity exercise (average VO_2 0.70 L.min^{-1}) this decline continued in water temperatures below 32°C, while for a higher intensity exercise (average VO_2 0.92 L.min^{-1}) rectal temperatures increased in water ≥28°C (401). These findings were supported by Israel et al. (1989) who found that 30 minutes of cycling during water immersion to the neck at 63% of VO_{2max} in 21.1°C and 25.3°C water did not elicit changes in core temperature, while 29.4°C water and 21.1°C land-based trials demonstrated similar increases in core temperature (+0.6°C water, +0.8°C land) (403). The effects of warmer water temperatures were examined by Carter et al. (2023) who observed that during immersion to the umbilicus, cycling against a progressively harder load increased core temperature modestly in 32°C water, while the same protocol in 38°C water substantially increased core temperature (+0.8°C) over 30 minutes (300).

These studies highlight that exercise can affect thermoregulation and change the point of thermoneutrality during exercise. It is important to note that these studies included young and healthy, relatively lean and mostly male individuals, so the impacts on females, older people and those with chronic disease are yet to be determined.

2.3.3.2 The physiological response to submaximal water-based exercise.

Submaximal intensity exercise is employed in most exercise programs for people with CHD (128, 174), and therefore the submaximal physiological response to exercise will be the focus of this review.

2.3.3.2.1 Cardiovascular responses

Acute water-based exercise in healthy individuals elicits similar changes to land-based exercise, although from an altered baseline, as cardiac output and stroke volume are elevated at rest and total peripheral resistance is reduced (23, 72). While heart rate can be lower during resting water immersion (see 2.3.2.2.3), increases during submaximal water-based exercise are similar to land-based exercise (23, 109). People with CHD generally exhibit similar patterns of change in haemodynamic variables during exercise as their healthy counterparts (44, 55, 110, 111).

Cardiac output

In healthy individuals, the pattern of cardiac output (305, 318, 361, 404), or cardiac index (324), increase during exercise is the same between water and land-based exercise. However, this often occurs from an elevated baseline when in water, due to the cardiac volume increase resulting from resting immersion, which can result in higher absolute values for water-based exercise (305, 319, 324, 404), although this is not universal (361). While the pattern of increase in cardiac output is similar between land and water-based exercise, the mechanism of increase may be different. Park et al. (1999) found that the increased cardiac output during water-based exercise (from resting immersion) was driven primarily by elevations in heart rate (as stroke volume was already elevated), compared with a combination of increased stroke volume and heart rate on land (305). In people with CHD the increase in cardiac index during immersion registered between that measured in people with CHF and healthy individuals, and demonstrated further increases during ‘jumping jack’ and swimming exercises (339). In healthy individuals, the increase in cardiac output with water-based exercise, compared to rest on land was +46%, and the increase from water-based rest to exercise was +11% (319). In people with CHD, Hanna et al. (1993) observed increased resting cardiac output during water immersion, which rose further during water-based exercise, however the absolute matched-intensity exercising values approximated those observed during land-based exercise (405). McMurray et al. (1988) observed the same pattern of increase in cardiac output for water and land-based matched intensity exercise in people with CHD, but the increase in absolute values with water-based exercise, compared to land-based exercise didn’t reach significance (406). The variable results may reflect small difference in the immersion temperatures (30°C (406) vs 31°C (405)), differences in immersion depth (xiphoid (406) and suprasternal notch (405)) or clinical variables/medications between cohorts.

Stroke volume

In healthy individuals, stroke volume was generally elevated at rest with water immersion (305, 319, 361, 404) and may increase further during water-based exercise (404), particularly during the initial onset of exercise (404), although this was not observed in all studies (319). In people with CHD, stroke volume was increased at rest, and during the initial exercise response during water-based exercise up to 40% of VO_{2peak} and during land-based exercise up to 60% of VO_{2peak}, with no significant differences in absolute values between water and land-based exercise (405).

In people with CHF, stroke volume increased with resting immersion, and while water-based exercise increased stroke volume from 52ml during resting immersion to 66ml this further increase did not reach statistical significance (319). Wide interquartile ranges and large standard deviations suggested there was significant variation in outcomes during water-based exercise, which may have impacted the significance of this finding given the relatively small sample size (n=13). There is likely a spectrum of responses between people with CHF dependent on the degree of cardiac impairment, with Meyer and Bücking (2004) finding increased stroke volume in people with moderate heart failure during resting water immersion to the neck, while in some patients with severe heart failure the left ventricle became dyskinetic and stroke volume failed to rise (340).

Heart rate

In healthy people, low to moderate intensity exercise (≤60% of VO_{2peak}) resulted in similar heart rate responses between land- and water-based exercise (324, 361, 404). During exercise at ≥80% of VO_{2peak}, heart rate was lower with water-based compared to land-based exercise (324, 404). Water temperature may mediate the heart rate response to water-based exercise. Pugh et al. (2015) reported that heart rate increased during 30°C water-based exercise to match land-based values (361), whilst Park et al. (1999) observed that the heart rate response to water-based exercise in 30°C water was lower than that in response to 34.5°C water (305). Furthermore, while heart rate increased during progressive exercise loading, the increase was lower during exercise at matched loads at 32°C, compared to 38°C (300).

In people with CHD, submaximal exercise heart rate was the same during water- and land-based exercise at 40, 60 and 75% of VO_{2peak} (405), while there was a tendency for a lower heart rate during low intensity exercise in the water (VO_2 <1.0 $L.min^{-1}$) (406), which equates to approximately 50% of VO_{2peak} for people with CHD. These findings indicate land-

based assessments can be used to guide heart rate for water-based exercise prescription in people with CHD, with this being most reliable at moderate exercise intensities.

Total peripheral resistance

Total peripheral resistance (systemic vascular resistance) was found to be reduced with water immersion compared to land-based measures (305, 361), and reduces further during both land and water-based exercise (305, 361). Park et al. (1999) observed a ~25% reduction in total peripheral resistance with land-based exercise, while resting water immersion in 30°C reduced resistance by 32% and in 34.5°C by 37% (305). Exercise elicited further 14% and 8% significant reductions in peripheral resistance with matched intensity exercise during 30°C and 34.5°C water immersion, reaching a total reduction of approximating 40% with water-based exercise (305).

In people with CHD, total peripheral resistance reduced with water-based exercise in proportion to workload (339, 406). While this occurred in the same pattern as during land-based exercise, the absolute values were consistently lower with water-based exercise (406), which may aid perfusion during exercise.

2.3.3.2.2 Blood pressure

Water and land-based exercise of matched intensity increased SBP to a similar extent in healthy individuals (305, 324, 404). Similar findings have been observed in people with CHD or CHF (405, 407). In males with CHD, an incremental cycle test immersed to the xiphoid resulted in a similar gradient of SBP increase during land-based assessment, compared with water-based exercise (when matched for VO_2), however the absolute values remained lower (406).

In healthy individuals, DBP did not change with moderate intensity land or water-based cycle ergometry (305, 404). However, at 80% of VO_{2max} there was a significant reduction in DBP for the land-based group compared to the water-based group (404). In people with CHD or CHF, DBP did not change from resting immersion to jumping jacks exercise (339). In contrast to this, water-based seated reciprocal unilateral knee extensions increased DBP in people with CHF and healthy individuals (319). This may be due to the different exercise protocols used, or different water temperatures.

In healthy people, MAP was greater during resting water immersion than non-immersed values, increased during exercise and remained greater than matched-intensity land-based low intensity exercise (361). In people with CHD, water-based exercise

increased MAP with increasing exercise intensity at a similar gradient to matched-intensity land-based exercise, however the absolute values of the water-based cycling were lower than the land-based cycling trial (406). The divergent MAP effects between these studies may reflect differences due to pathology, age, the exercise intensity (low intensity compared to progressive protocols), or potentially a greater vasoconstrictive response (as cutaneous vascular conductance was reduced and total peripheral resistance increased alongside the greater MAP response) (361). This may indicate higher sympathetic activation with the water-based protocol. Despite both studies occurring in 30°C water, people were exposed to this for longer before starting exercise in the Pugh et al. (2015) study (9 minutes to fill the tank and 5 minutes of rest) (361), whereas this did not occur in the McMurray study of people with CHD. Interestingly, McMurray et al. noted that the cool temperature would not allow for true resting baseline state to be achieved for the accurate measurement of physiologic outcomes (406), so the protocol was commenced sooner and progressed to a higher intensity, which may have prevented a vasoconstrictive response.

Rate pressure product, an indicator of myocardial oxygen demand derived from SBP and heart rate measurements, tended to be reduced during low intensity (VO_2 <1.4L.min^{-1}) water-based exercise, compared to land-based exercise, in people with CHD (406).This may indicate there is less stress to the heart during exercise at lower intensities while immersed in water.

2.3.3.2.3 Peripheral arterial function

Only a few studies have investigated the effect of acute water-based exercise on arterial wall shear stress and endothelial function, with samples being mostly younger males (298, 408-410). During resting water immersion, shear stress and blood flow were found to be influenced by water temperature (299, 313, 322), although only one study has investigated these influences during exercise (298).

Carter et al. (2023) investigated the effects of cycling during 32°C and 38°C water immersion to the umbilicus on brachial artery shear stress in young, healthy people (mean age 24 years, mean BMI 22.8kg.m^{-2}) (298), and included a land-based comparator. The prescribed workload was identical between conditions (+5kg, +10kg, +15kg), which precipitated differences in oxygen consumption between water and land-based trials (+15.8ml.kg^{-1}.min^{-1} and +17.2ml.kg^{-1}.min^{-1} for 32°C and 38°C water immersion, compared to +9.8ml.kg^{-1}.min^{-1} during land-based exercise at the highest workload (298)). These differences are likely due to the impact of increased drag resistance from water immersion (see 2.3.1.4). The

difference in exercise intensity between the land and water conditions renders the interpretation of shear stress changes between land and water exercise conditions more challenging, as there may be different exercise-induced changes in central haemodynamics in addition to the changes induced by water immersion.

Water-based cycling exercise in 32°C water has been shown to increase brachial artery antegrade shear, however, due to a simultaneous increase in retrograde shear stress, total shear was not significantly different to land-based exercise (298). When water temperature increased to 38°C there was a significantly greater increase in total shear stress compared to land and 32°C water-based exercise, driven by an increase in antegrade shear stress with a simultaneous attenuation of retrograde shear stress (298). These changes were associated with a +0.3°C increase in core temperature with 32°C water-based exercise and a +0.8°C increase during 38°C water-based exercise, while core temperature during land-based exercise was unchanged (298). Land-based exercise slightly increased total shear, but to a lesser extent than 38°C water-based exercise (298).

While increased retrograde shear in healthy, young males was associated with acute endothelial impairment (411), other findings suggested this effect does not occur in older males (412) and that the antegrade shear elicited by a stimulus likely plays a greater role in mediating the changes in FMD (413).

Although acute exercise has been found to impair post exercise FMD, likely due to SNS influences (414), exercising in warm (38°C) water while immersed to the umbilicus increased 30 minute post exercise FMD from baseline (from 6.2±1.9% to 8.5±2.7%), while there were no changes in the 32°C or land groups (298). Ayme et al. (2014) examined the impact of one hour of low intensity (35-40% VO_{2peak}) cycling in 32°C water (immersed to the xiphoid process), or on land, in young, healthy men, finding an increased brachial artery diameter 40 minutes after exercise cessation, while not significantly changing FMD from pre-exercise values with either modality (408).

In contrast to the Ayme at al. (2014) and Carter et al. (2023) data, studies involving at least moderate intensity treadmill exercise have found latent post exercise impairment in FMD (409, 410). Hashimoto et al. (2019) investigated the impact of 30 minutes of walking exercise at 60% of heart rate reserve (137-138beats.min^{-1}) in healthy, young men, and observed reduced FMD 30 minutes after the land-based trial, while no effect was observed for water-based exercise (30°C, xiphoid) (410). At 60 minutes post exercise, while FMD had recovered to be similar to pre exercise values in the land-based condition, FMD in the water-

based exercise group was significantly higher (410). In males with hypertension and pre-hypertension, Joubert et al. (2018) investigated the impact of a land or water-based treadmill exercise session at 60% of VO_{2peak} on FMD one hour after exercise (409). The exercise bout lasted for a mean time of 30 minutes on land, and 29 minutes in the water, until 300 kilocalories were expended (409). The water-based treadmill session occurred in 30-31°C water immersion to the xiphoid (409). One hour after exercise, FMD tended to be reduced after land-based treadmill exercise (-1.3%, 90% CI -2.7% to 0.2%) and improved after water-based exercise (+1.2%, 90% CI -0.07% to 2.5%), with a between group difference in favour of water-based exercise (2.5%, 90% CI 0.6% to 4.4%) (409).

While post exercise FMD in the water-based trials were consistently unaffected, the differences in the land-based responses may be related to differences in exercise modality (treadmill versus cycle ergometer) leading to differences in shear stress pattern, or alternatively, may be due to differences in intensity (light-to-moderate compared to moderate-to-heavy). Changes in SNS activation may impact the latent FMD response to exercise. Water immersion is associated with sympatho-suppression (317). Exercise at 75% of VO_{2peak} has been observed to acutely impair FMD responses immediately post-exercise, and this was found to be related to sympathetic nervous system activation, as the administration of an α_1-adrenoreceptor blocker prevented the decline in FMD post exercise, resulting in FMD increasing from 4.7% pre-exercise to 6.3% post exercise (414). Alterations to sympathetic function may go some way to explain the latent response still present one hour after exercise in people with hypertension, as this condition is associated with an overactivity of the sympathetic system (365), which may take longer to resolve. Alternatively, differences may be due to a change in the shear stress stimulus during exercise, although further research is needed to determine if this is the case. How the acute water-based exercise and post-exercise changes in shear stress and FMD impact training adaptations in people with CHD remains to be established.

2.3.3.2.4 Cerebrovascular function

Resting water immersion was found to increase MCAv and PCAv (316). From this elevated baseline, Pugh et al. (2015) examined low intensity stepping exercise, while immersed to the right atrium in 30°C water, observing increased MCAv and PCAv in the same pattern as during land-based exercise (361). The increase in MCAv was ~10% higher than land-based values, with PCAv increasing ~9% compared to land-based values (361). These changes were associated with increases in mean arterial blood pressure and the

partial pressure of expired carbon dioxide (CO_2), which may be two potential mechanisms mediating this increase.

Incremental water-based treadmill exercise increased MCAv during 32°C immersion to the iliac crest in healthy, young (mean age 27 years) participants, compared to land-based treadmill walking, and provoked a faster rise to peak MCAv in the water group (4 minutes vs 10 minutes) (415). Furthermore, water-based walking elicited an increase in MCAv that was the equivalent of running on the land-based treadmill at estimated 65% VO_{2max} (415). Water immersion depth during steady-state exercise did not significantly vary MCAv between mid-thigh, iliac crest or xiphoid levels, while heart rate progressively reduced with increasing depth (415). This study highlights that water-based exercise can elicit greater changes in MCAv earlier in exercise programs, at lower heart rates and exercise intensities than land-based exercise. This is promising for improving cerebrovascular function in people with conditions such as CHD, as both aerobic capacity (VO_{2peak}) and aspects of cognitive function (short term memory, working memory, long term verbal memory, cognitive inhibition and flexibility) are lower in people with CHD, compared to age-matched healthy controls (416).

Underwater cycling for three, 10 minute stages of increasing resistance in 32°C and 38°C water immersion to the umbilicus in young, healthy participants (mean age 23.8years, BMI 23.0kg.m^2) increased MCAv the initial stage of exercise with 32°C immersion, which was maintained for the remainder of the protocol (300). The MCAv of the 32°C water immersion group was elevated compared to the land-based group and the 38°C water immersion group throughout the protocol (300). Warm (38°C) water-based exercise attenuated the increases in MCAv seen at cooler temperatures, and this attenuation occurred in the context of similar increases in VO_2 and $P_{ET}CO_2$ (300). Exercising in 38°C also reduced the increase in MAP during exercise, and led to a greater increase in core temperature and peripheral artery blood flow than 32°C immersed exercise (300).

It appears the optimal water temperature for eliciting peripheral and cerebral vascular effects is different, with exercising in water temperatures of less than 32°C eliciting positive cerebrovascular changes (300, 361, 415), while exercising in 38°C water was more conducive to increasing brachial artery shear and post-exercise FMD (298) . Determining the optimal water depth and temperature during exercise to enhance both peripheral and cerebral vascular outcomes has not been established. Optimising both cerebral and peripheral aspects of vascular health is important for people with CHD, as impairments in peripheral arterial function have been associated with poorer survival outcomes (230, 417), and there is a strong link between CHD and increased risk of cognitive impairment (255).

2.3.3.2.5 Musculoskeletal system activation and pain responses

Determining the optimum method to apply resistance and induce strength changes are important considerations for training programs. Furthermore, given that musculoskeletal comorbidities are common in people with CHD (3, 135), ascertaining the impact of an exercise modality on musculoskeletal comorbidities and pain is important when considering exercise program design.

Colado et al. (2013) examined upper limb and core muscle activation with shoulder extension exercises with different resistance devices and water depths (418). No differences were found between the devices used (drag glove, a perforated disc to increase surface area, foam dumbbell and floating wristband) on latissimus dorsi or erector spinae activation, although wrist floats tended to produce a larger percentage of maximal muscle activation for the rectus abdominis. Compared to xiphoid depth immersion, clavicle depth immersion reduced latissimus dorsi activation and non-significantly reduced rectus abdominus activation, with erector spinae activation unchanged (418). This would suggest a shallower depth may be preferential for increasing muscle activation. A similar study conducted with different combinations of devices during hip adduction at maximal velocity while immersed to the xiphoid process again found no differences between device type (419). The contralateral oblique to the moving limb displayed greater activation than the ipsilateral side (419), highlighting the role of core activation for stabilisation during water-based exercises. In an examination of different rehabilitative exercises, muscle activation between land and water-based exercises (28°C) was similar for 66% of comparisons, with increased activation with water-based exercises in 5% of cases and with land-based exercise in 29% of cases (420). Furthermore, during rehabilitative exercises in the water, hip abduction/adduction and hip flexion/extension exercises produced the greatest activation in the gluteal muscle groups, even compared to squats (421), indicating this type of exercise is worth consideration for inclusion in water-based strengthening programs.

Gait changes during water walking (150). When participants were asked to walk at a comfortable pace, water-based gait analysis during immersion to the xiphoid found significantly slower stride period compared to land-walking, with no impact on stride length, while vertical ground reaction force was lower (150). Leg joints exhibited similar ranges of motion between land and water walking, though the angular velocities were lower with water walking at a comfortable pace (150). Compressive and shear joint forces were significantly lower with water walking, compared with walking on land (150). The reduction in shear and compressive joint forces of the ankle, knee and hip suggests that water-based exercise to

the xiphoid provides a low impact option for exercise, which may make exercise more comfortable for people with CHD and musculoskeletal comorbidities.

The impact of 11 acute musculoskeletal rehabilitation exercises in water with comparable exercises on land was investigated in people with chronic lower back pain (n=20) (420). Pain was provoked in 7.7% of land-based exercises, compared to 3.7% of water-based exercises, although the mean visual analogue pain scores were not significantly different (1.8±1.0 immersed, 2.4±1.6 on land) (420). A subsequent study in 20 males with chronic lower back pain assessed 26 different water-based exercises, with reported pain in 2.8% of all exercises and mean non-zero pain level was 2.0 on the visual analogue scale (421).

In summary, drag resistance and floatation equipment have tended to produce similar effects when moved at maximal pace in young, healthy people (418, 419), and ground reaction, joint shear and compressive forces were lower during comfortable-paced water walking (150). Water-based exercises were associated with lower pain provocation in people with chronic lower back pain (420), while muscle activation for gluteal muscles during water-immersed exercise can be optimised with hip extension and abduction exercises (421). These changes suggest water-based exercises are less likely to provoke musculoskeletal comorbidities, particularly for lower limb exercises and walking, and muscle activation can be successfully increased through a range of exercises and the addition of water-based resistance equipment.

2.3.4 Effects of water-based exercise training in people with coronary heart disease

In people with CHD, upright, water-based exercise training has been examined as an inpatient, high frequency, short-format intervention (2-3 weeks duration) (422-425), as well as in a longer duration, less intensive format (206, 426-428). A variety of exercise types have been discussed in the literature, including combined land and water programs (424, 425, 427), separated strength and aerobic sessions (206, 422, 423, 426) and aerobic training with games (428).

Aerobic capacity and exercise tolerance

A meta-analysis of the effects of water-based exercise training in people with CHD included six studies with 189 participants (91% male) (429). Exercise test duration was measured in two studies (n=41) with water-based exercise training having a greater effect than a non-exercising control (mean difference +1.2 minutes, 95% CI 0.5-1.9 minutes) (429).

Furthermore, improvement in peak power output with combined land and water-based exercise was greater than land-based exercise alone (mean difference 11.0W, 95% CI 4.0-18.5W) (429).

While improving exercise tolerance is important for people with CHD (187, 430) measuring VO_{2peak} is the gold standard for assessing aerobic capacity (431). There was a similar improvement in VO_{2peak} seen with three weeks of high frequency land-based or combined land and water-based exercise (424, 425), with meta-analysis finding no significant difference between interventions (mean difference 1.97ml.kg^{-1}.min^{-1}, 95% CI -0.94-4.88ml.kg^{-1}.min^{-1}) (429). Further studies have reported improvements in VO_{2peak} with completely water-based training programs. A two week training program led to 27% and 15% increases in VO_{2peak} with water and land-based programs, respectively, and these changes were significantly different between groups and compared to a control group (422). Additionally, 24 weeks of water walking increased VO_{2peak} by +2.0ml.kg^{-1}.min^{-1}, with a similar increase in the land-based walking group (+2.3ml.kg^{-1}.min^{-1}) and no change in the control group (-2.5 ml.kg^{-1}.min^{-1}) (427). Finally, 4 months of water-based training resulted in an 8.4% increase in VO_{2peak}, although this was not significantly different to the change in a non-exercising control group.

These studies support the use of water-based exercise programs for improving VO_{2peak} in people with CHD. However, no studies to date have evaluated the effects of water-based circuit training, compared the effects of water-based with gym-based circuit training, nor have there been any exercise training programs studies for a duration longer than 3 weeks that have examined changes in VO_{2peak} compared to gym-based exercise.

Muscular strength

Only a few studies have examined strength outcomes. Meta-analysis calculated that water-based training increased total body strength, compared to a non-exercising control (2 studies, n=41 participants) (429). Additionally, Volaklis et al. (2007) observed a similar improvement between land and water-based programs (206). These analyses suggest that water-based exercise can improve muscle strength in people with CHD who are inactive, and there are similar effects to land-based training.

Body composition

Meta-analysis of studies that assessed body composition with water-based exercise compared to control found no differences in body weight (n=3 studies, 67 participants) mean

difference -1.2; (95% CI -4.7-2.4), or BMI (n=2 studies, 46 participants) mean difference 0.45; 95% CI -1.31-2.21), but calculated sum of skinfolds were improved by aquatic exercise over control (mean difference -8.6; 95% CI -12.3 to -4.8) (429). These analyses indicate that global measures of body composition were unaffected by water-based exercise training, however more specific indices, such as body fat, improved. This highlights the need for specific measures of body composition when assessing training interventions in people with CHD.

Vascular function and other outcomes

To date, only short duration studies have investigated the impact of water-based training on endothelial function in people with CHD. Vasić et al. (2019) reported that both short-term, high frequency (2 week, 24 session) water and land-based exercise training programs improved FMD in people with recent MI or revascularisation procedure (within 2-4 weeks) compared to a wait-list control group, with no significant difference between training groups, although FMD in the land-based group was much lower than the other groups at baseline (5.5% compared to 7.2% and 7.0%) (422). Impaired baseline FMD is associated with a greater prospect of improvement with exercise (432), so whether the degree of improvement would have been the same between groups in a more homogenous sample is a point of contention. A further short-term, high-frequency, study comparing combined water and land-based exercise to land-based exercise in people with CHD (3 weeks, 10 sessions per week) observed increases in plasma nitrate (a metabolite of endothelial function) with the combined training, but not with land-based training alone (424). The changes observed by Mourot et al. (2009) have been supported by observed differences in endothelial function, or markers of endothelial function, between land and water-based exercise in other populations (see Section 2.3.5). While the short-term studies suggest water-based exercise is at least as effective as land-based exercise for improving endothelial function in people with CHD, the high frequency (twice-daily) format of these studies may not be sustainable for the many patients, and the effects of longer-duration, less frequent, water-based exercise programs in people with CHD are yet to be examined.

The effect of water-based exercise training on heart rate variability has been investigated over the short- (2 week) and longer-term (16-weeks) (423, 428). The main findings from the short-term training program were a slightly increased resting heart rate, an increase in the low to high frequency ratio and an increase in the non-linear short-term scaling exponent α1 from detrended fluctuation analysis (423) (these tests are outlined in more detail below).Given other markers of SNS function are elevated in the first six months

after an MI (433), these measures may have confounding factors other than training, including natural recovery, and from the addition of new medications post coronary event, such as beta blockers that can alter heart rate variability (434). While historically lower heart rates have been associated with improved myocardial oxygenation (435), recent research suggests heart rates that are too low, as well as heart rates that are too high, are both associated with an increased risk of death in people with CHD (436) and this has been reflected on overall population data (437). A lower low to high frequency ratio has historically been associated with increased parasympathetic dominance over 24 hour analysis, which would be favourable for people with CHD given the elevated sympathetic responses (433), however recent research has questioned this interpretation of the ratio and the appropriateness of the measure's use as a short-term metric has not been established (394). The short-term scaling exponent α1 from detrended fluctuation analysis has been correlated with baroreceptor reflex, although this metric was designed to analyse a longer time series than the data from this paper (394). As the changes observed during the short-duration recordings were mixed (423), a study investigating the impact on longer-duration recordings of HRV (such as 24 hour recordings) may be of value for clarifying the effects of short-term water-based exercise training on HRV, as longer duration of recordings have formed the evidence base underlying the interpretation of these metrics (394).

In a longer-term study, Fiogbé et al. (2018) observed that 16-weeks of water-based training did not change time or frequency domain HRV data, though improvements were seen in non-linear metrics (428). These improvements with water-based training may indicate improvement in cardiac autonomic modulation in people with CHD with water-based exercise training. However, this study had no land-based training comparator, so whether the water immersion, exercise or a combination of both, had mediated these changes is unknown.

Summary

While there are limited studies investigating water-based exercise training in people with stable CHD, the findings to date highlight the potential for water-based exercise training to improve indicators of exercise tolerance, muscle strength and body fat. Water-based circuit training, involving alternating aerobic and resistance stations within one session, has not been examined in the literature for people with CHD and may be beneficial for efficiently including both aerobic and resistance modalities within sessions to assist patients meeting exercise guidelines. Furthermore, studies of longer than 3 weeks duration have not examined the impact of water-based exercise on endothelial function, and no studies have

investigated the impact of water-based exercise training on cerebrovascular outcomes for people with CHD. Additionally, no randomised, controlled trials have compared water-based training to traditional, gym-based circuit training exercise on VO_{2peak} responses.

2.3.5 Effects of water-based exercise training on peripheral and cerebrovascular outcomes in other populations

Water-based exercise and swimming have been found to improve arterial health in other clinical populations, although the impact in healthy people has been mixed. Studies investigating swimming training have demonstrated increased FMD compared to cycling exercise (438) and compared to inactive control groups in older adults (439) and people with hypertension or pre-hypertension (440). Additionally, improvements in arterial and carotid stiffness have been found with swimming, but not cycling exercise in adults with arthritis (438). While these swimming studies are promising, the effect of the horizontal position can affect cardiac pressures in people with cardiac conditions (340).

In upright water-based exercise training studies, improvements in vascular function have been seen in clinical populations. In people with type 2 diabetes, both land and water-based cycling (36°C, hip level immersion) improved FMD (land: 3.4% to 5.6%; water: 3.4% to 6.2%), while microvascular function only improved with water-based cycling (441). Additionally, Nuttumonwarakul et al. (2014) reported improvements in microvascular function with 34-36°C water exercise, although these effects were not evident in the land-based exercise group (442). Meanwhile, water-based circuit training exercise increased FMD in people with type 2 diabetes compared to a non-exercising control group (443). In people with peripheral arterial disease, arterial stiffness, assessed using leg pulse wave velocity, was improved with water-based training, to a greater extent than with land-based training (444). In people with resistant hypertension water walking at a low to moderate intensity increased plasma NO (a metabolite of endothelial function), while reducing blood pressures, plasma renin and endothelin-1, but failed to increase peripheral arterial tonometry measures of reactive hyperaemia (a measure of endothelial function) (445).

While the studies in clinical populations generally indicate a favourable vascular adaptation response to water-based exercise, responses in healthy individuals have been mixed (446, 447). Water-walking for 24 weeks in a 28-30°C pool was compared to a land-based walking in healthy older adults and did not find any significant improvements in FMD over time within any group, however the land-based group demonstrated greater improvement than a sedentary control group (446). The difference between a healthy

population and clinical cohorts may relate to disease-related differences in endothelial function that occur with CVD (228, 448), the different patterns of shear stress from different exercise modalities (449), or differences related to the timing of assessments, as FMD typically returns towards baseline as structural remodelling occurs in longer duration studies (232). Furthermore, in healthy, sedentary adults, water-based treadmill training three times per week over 12 weeks in 33°C water immersion to the sternal notch at 60-85% of VO_{2max} induced a 31% increase in vastus lateralis eNOS expression (a key regulator of endothelial function (450)), whilst there was no change with the land-based treadmill group (447), supporting the studies in clinical populations that found differences between training modalities. Water temperature may have played a role in some of the differences between responses in healthy individuals, as differential impacts on shear stress have been observed with different temperatures (298, 299).

The effect of water-based training on cerebrovascular outcomes has not been well examined in the literature. A 24 week study comparing land and water-walking interventions in healthy older adults found no changes in resting MCAv or neurovascular coupling response with either modality, although there was an improvement in normalised gain during dynamic cerebral autoregulation assessment in the very low frequency spectrum with water-based walking, compared to land-based walking (451). Cerebral autoregulation represents the ability for the brain to maintain perfusion despite changes in systemic blood pressure, with the gain representing the degree of attenuation in the MCAv signal related to the blood pressure, with lower gain thought to represent more effective regulation (452). Further research needs to be conducted to determine the impact of water-based exercise in a range of populations.

2.3.6 Considerations for water-based exercise prescription

2.3.6.1 Safety

The main safety considerations that have been investigated in the literature include elevated filling pressures in people with heart failure and the risk of arrythmia during water immersion.

Meyer and Bücking (2004) noted that pulmonary artery and capillary pressures increased during immersion, particularly during swimming, although remained below pathological values when immersed to the xiphoid or lower (340). In some patients with severe CHF, changes in cardiac filling may have resulted in the left ventricle becoming dyskinetic in a small (n<5) number of participants, as the systolic length diameter was observed to increase

more than the diastolic length diameter, with a failure to increase stroke volume, resulting in a reduction in stroke volume, although participants reported feeling well throughout immersion (340). Despite the safety concerns regarding water immersion in people with CHF, several studies have conducted training programs in this population with no ill effects (424, 453, 454) and studies have found acute improvements in cardiac function during immersion (319, 336).

The risk of arrythmia with water immersion and water-based exercise has been examined for people with CVD. Moderately cold (22°C) water immersion led to an increase in premature ventricular contractions in people with CHF, compared to 32°C immersion or the average over a 24 hour period when not in the water, likely due to increased sympathetic activity associated with being immersed in cold water (338). There was no significant change in premature ventricular contractions in people with CHD at either 22°C or 32°C from land-based recordings (338), and the highest form of ventricular arrythmia recorded was a short sequence of bigeminy out of the combined CHD and CHF cohort. These results suggest either temperature is appropriate for people with CHD and normal ventricular function. Assessment of oxygen consumption requirements for swimming and upright water-based exercise found upright water-based jumping jacks required a VO_2 of 10.7±3.1ml.kg^{-1}.min^{-1} in people with CHD, while swimming (stroke type not specified) required 12.4±3.5ml.kg^{-1}.min^{-1}, with the authors suggesting that for people with stable CVD a VO_{2peak} ≥15.0ml.kg^{-1}.min^{-1} and an anaerobic threshold ≥10ml.kg^{-1}.min^{-1} is recommended for participating in water-based exercise activities (339).

Further research on the impact of water-based exercise was undertaken in males with stable CHD (n=62, post-MI, mean age 51 years) (455). The cohort took part in an eight week swimming training program twice per week for 55 minutes per session in 28-30°C water, and had Holter monitoring for 24 hours on land, and twice during a water-based exercise session (at the start and end of the program) (455). The water-based Holter readings were compared to a 55min and 40min period of the 24 hours recording (455). VO_{2peak} increased by 15.3% over the training program and was maintained 12 months later, the mean number of ventricular ectopic beats over the 40 and 55 minute exercise and total session blocks were not significantly different to non-immersed values, and while there was an increase in supraventricular ectopic beats during the sessions, there were no complex arrhythmias or signs of myocardial ischaemia during training (455). During water-based training sessions, ventricular ectopic beats and supraventricular ectopic beats occurred more frequently than during cardiopulmonary exercise testing and activities of daily living

(455). Given the water temperature was relatively cold in this study, and there was a lot of low-movement time in the session (approximately 20-30 minutes), there may have been a cooling effect and increase in sympathetic activity in the participants which may have affected the findings. Additionally, swimming is a different stimulus on the heart to upright immersion (339, 340), because of the additional fluid shift in the horizontal position, which may have impacted findings.

From the literature to date, a conservative approach for safely conducting water-based exercise in people with stable CHD would be to include baseline cardiopulmonary exercise testing, (to screen for ischaemic changes with exercise and ensure an adequate VO_{2peak} for water-based exercise), and then performing any program or immersed exercise up to the xiphoid depth in an upright position in ≥32°C water.

2.3.6.2 Resistance exercise prescription in water-based exercise

Resistance in the water is primarily applied through utilising the physical principles of water immersion to leverage the effects of buoyancy and drag resistance. Buoyancy resisted exercises that utilise equipment of low density but high volume (e.g. foam) which float, can be used to add resistance when they are pulled down into the water, while equipment that increases surface area can increase drag resistance (456).

Issues identified with buoyancy resistance include the number of devices needed for different resistance levels and that certain actions are difficult to perform against buoyancy resistance (as the direction of movement needs to be directed towards the floor for maximal resistance) (456). As such, devices that increase drag resistance have been developed as an option. We have designed and utilised a set of these devices previously in a project involving people with type 2 diabetes, where lower limb strength was increased compared to control (443).

An overview of the effects of drag resistance is provided in Section 2.3.1.4, with the drag force calculation outlined in Equation 3 (force of drag is the product of the drag coefficient, half the water density, the square of the velocity and the frontal surface area) (302). The variables that can be modified in training programs to increase drag force are the frontal area of the body (frontal surface area), by adding a flat device on top of the limb, such as a paddle or boot (301, 456), and through increasing the velocity of the movement (456). A doubling of the velocity equates to a quadrupling of the drag force, highlighting increasing the speed of movement as a feasible method for increasing load. A practical example of

calculating the drag force and drag coefficient has been provided by Pöyhönen et al. (2000), who used a hydro-boot and dynamometer to establish the drag coefficient and effects of different movement velocities (301). They found that the resistance of the bare leg, below the knee approximated 61N, while the addition of a boot which increased the surface area, moving at the same speed, increases the resistance to 270N (301).

Factors to control drag force during water-based exercise training include;

- Controlling the cadence of the movement
- The size of the device (frontal surface area)
- The position of the device on the limb
- The position of the moving limb segment

(456).

Furthermore, cadence should be prescribed based on the desired difficulty and number of repetitions, and timing devices (such as a metronome) can be used to monitor this (456). Progressing exercise intensity can be achieved by using equipment with a larger surface area or increasing the speed of movement (456). Compared to isokinetic land-based exercise using a dynamometer, water-based exercise utilising drag resistance demonstrated an earlier reduction in concentric activation of the agonist muscles, and greater activation of the antagonist muscles to decelerate the limb towards the end of the movement range (457). This period of co-contraction may be particularly useful for increasing joint stabilisation, helping to promote functional strength and stability and may be useful for rehabilitating injured joints, where co-contraction is desirable.

Limitations of using drag resistance include the core control or stability of the participant, thus potentially restricting movement speed or equipment size (456), and that there may be a lower maximal force generation capacity of some muscle groups with water-based exercise, compared to isokinetic or isometric dynamometry on land (457). However, not all muscle groups were affected by this reduction (457), and modifications, such as changing the position the exercise is performed in to be perpendicular to the lift force, may be utilised to optimise drag resistance (457). Furthermore, in training programs for people with CHD it is rare to exercise at a 1RM level of resistance, meaning compensatory strategies, such as moving faster in the water to work at a higher relative load, could likely counteract this potential reduction in the percentage maximum the person is achieving in the water for any affected exercises.

In summary, water-based resistance training can be applied through a variety of means, with drag-resistance exercises able to be performed for a greater variety of movements than buoyancy resisted exercises. Guidelines have been suggested for implementing drag-resisted exercise, focussing on controlling the range of movement, equipment size and speed of movement to allow programs to be adequately monitored, compared and progressed.

2.3.7 Summary

Coronary heart disease is a significant global health issue (27) , with a profound clinical, social and financial burden (44, 48, 50). Coronary heart disease occurs when there is a narrowing or occlusion of the coronary arteries, restricting blood flow to the myocardium, and can lead to tissue damage if not reversed (1, 6). This process is often precipitated by endothelial dysfunction, where the function of endothelial cells lining the lumen of arteries becomes impaired, promoting a pro-atherogenic environment which is conducive to the migration of lipids and other substances into the blood vessel wall (1, 8). This process can narrow arteries, restricting blood flow to the myocardium and if a plaque ruptures, the affected coronary artery can be occluded, leading to a MI (1, 6). Accordingly, an increased risk of mortality has been observed in people with CHD and impaired endothelial function (417). While MI survival and incidence rates are improving in many developed nations (5) (34), the rapid ageing of the population (38) and elevated prevalence of CHD in older adults (5, 39) highlights that CHD will continue to be a significant health issue into the future.

Cardiac rehabilitation and secondary prevention strategies are associated with improvements in morbidity and survival (169-172), with exercise and physical activity key components of these programs (128, 174). Both aerobic and resistance exercise training are recommended for people with CHD (128, 174, 175), and a combination of these modalities has been observed to be more effective than either in isolation (201, 205). Combined aerobic and resistance circuit training incorporates both modalities within one session, facilitating patients to achieve exercise guidelines in a time-efficient manner, and this approach has demonstrated benefits to a range of health outcomes, including aerobic capacity (210-212), muscular strength (211, 212), body composition (211) and endothelial function (209, 458) when conducted as a gym-based program for people with a range of chronic health conditions. Furthermore, this approach has been utilised in a water-based environment in people with type 2 diabetes, improving strength, aerobic capacity and endothelial function outcomes compared to a control group (443).

Despite the benefits of regular exercise and increasing physical activity (186, 220), the uptake and maintenance of exercise is often sub-optimal in people with CHD (269-272). Studies investigating the barriers to exercise in people with CHD and other chronic disease have found that common barriers include insufficient time, low motivation, health concerns, particularly around musculoskeletal comorbidities and falls risk, as contributing factors (181, 284). Musculoskeletal comorbidities affect up to 60% of people with CHD (3, 135, 137), suggesting the extent to which this comorbidity may impact on exercise participation is significant. New exercise training options that help to address these barriers are needed to facilitate an increase in exercise participation.

If proven to be efficacious, water-based exercise training is a promising strategy to support exercise in people with CHD and may be especially beneficial for endothelial function. The physical properties of water provide unique features that can impact on exercise. Buoyancy aids in supporting the body in the water and reduces the weight bearing load on the lower limbs and spine (150, 292), with a reduction in joint compressive and shear forces (150), which, combined with benefits to pain responses (385, 386, 420, 459), may make exercise more comfortable for people with arthritis or musculoskeletal issues (459). Furthermore, the support from buoyancy and influence of drag resistance may make water-based exercise more appealing to people at risk of falling, and an elevated falls risk has been noted in people with CHD (287) and is associated with poorer health outcomes (224). Finally, the hydrostatic and thermal effects of water immersion can assist in venous return, cardiac preload and reducing sympathetic influence on the cardiovascular system (317, 324, 363), which can result in increased cardiac output, reduce peripheral resistance and increase peripheral and cerebral blood flow (298, 305, 316, 361, 415). Limited studies have assessed the changes to peripheral and cerebral blood flow during exercise and these impacts are yet to be investigated in people with CVD. However, if the acute changes seen in healthy individuals also occur in people with CHD, water-based exercise may provide a mechanism for additive benefits to arterial health through increasing exercise induced shear stress, a potent mechanism for improving endothelial function (233).

The only studies in water-based exercise training in people with CHD that have investigated the impact on arterial health have been in-patient, short duration, high frequency (twice daily) rehabilitation blocks (2-3 weeks duration) (422, 424) and only one has used a direct measure of endothelial function (422). While the format improved health outcomes in the short term (422), the high frequency water-based exercise training component would likely be unsustainable for patients as an ongoing modality. Whether

longer duration, less frequent, water-based exercise training programs can benefit cerebrovascular and peripheral endothelial health in people with CHD is currently unknown. Furthermore, whether a program of combined aerobic and resistance water-based circuit training, which helps to meet exercise guidelines for both exercise modalities, is effective for improving health outcomes for people with CHD has not been established. Current, longer duration studies in water-based exercise training for people with CHD either do not include resistance training (427, 428), lack a traditional exercise comparator (426, 428), or fail to utilise the gold standard measures for assessing aerobic capacity (VO_{2peak}) (206, 428), which is strongly associated with survival outcomes in people with CHD. Moreover, the effects of water-based exercise training of greater than three weeks on peripheral vascular or cerebrovascular outcomes has not been conducted in this cohort.

The current thesis addresses these gaps in the literature through a randomised, controlled trial of water-based circuit training, compared to traditional gym-based circuit training, in people with stable CHD. The project assessed a comprehensive range of outcome measures including traditional risk factors, functional outcomes and measures of peripheral and cerebrovascular health and function to determine whether water-based exercise is a suitable alternative to gym-based exercise. Broadening evidence-based exercise training options, to modalities such as water-based exercise, may increase the uptake of exercise, especially for the many patients with CHD who find traditional gym-based exercise difficult to perform, or not to their preference.

2.4 References

1. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
2. Australian Institute of Health and Welfare. Women and heart disease: cardiovascular profile of women in Australia. Canberra: AIHW; 2010.
3. Boyd CM, Leff B, Wolff JL, Yu Q, Zhou J, Rand C, et al. Informing clinical practice guideline development and implementation: Prevalence of coexisting conditions among adults with coronary heart disease. J Am Geriatr Soc. 2011;59(5):797-805.
4. World Health Organisation. Global Health Estimates 2019: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva: World Health Organisation; 2020.
5. Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts. Canberra: AIHW; 2023.
6. Falk E, Shah PK, De Feyter P. Ischaemic Heart Disease. London: Manson Publishing; 2009.
7. Australian Institute of Health and Welfare. Transition between hospital and community care for patients with coronary heart disease: New South Wales and Victoria 2012-2015. Canberra: AIHW; 2018.
8. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of atherosclerosis. Int J Mol Sci. 2022;23(6):3346.
9. Leloup AJA, Van Hove CE, Heykers A, Schrijvers DM, De Meyer GRY, Fransen P. Elastic and muscular arteries differ in structure, basal NO production and voltage-gated Ca2+-channels. Front Physiol. 2015;6:375.
10. del Monte-Nieto G, Fischer JW, Gorski DJ, Harvey RP, Kovacic JC. Basic biology of extracellular matrix in the cardiovascular system, Part 1/4: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(17):2169-88.
11. Sandoo A, van Zanten JJ, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. Open Cardiovasc Med J. 2010;4:302-12.
12. Gnasso A, Carallo C, Irace C, De Franceschi M, Mattioli P, Motti C, et al. Association between wall shear stress and flow-mediated vasodilation in healthy men. Atherosclerosis. 2001;156:171–6.
13. Buga G, Gold M, Fukuto J, Ignarro L. Shear stress-induced release of nitric oxide from endothelial cells grown on beads. Hypertension. 1991;17:187- 93.
14. Koller A, Sun D, Kaley G. Role of shear stress and endothelial prostaglandins in flow- and viscosity-induced dilation of arterioles in vitro. Circ Res. 1993;72(6):1276-84.
15. Green DJ, Dawson EA, Groenewoud HM, Jones H, Thijssen DHJ. Is flow-mediated dilation nitric oxide mediated? A meta-analysis. Hypertension. 2014;63(2):376-82.
16. Lamas S, Marsden PA, Li GK, Tempst P, Michel T. Endothelial nitric oxide synthase: molecular cloning and characterization of a distinct constitutive enzyme isoform. Proc Natl Acad Sci U S A. 1992;89(14):6348-52.
17. Radomski MW, Palmer RMJ, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet. 1987;330(8567):1057-8.
18. Kubes P, Suzuki M, Granger D. Nitric oxide: an endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci USA. 1991;88:4651-5.
19. Garg U, Hassid A. Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest. 1989;83:1774-7.
20. Chia PY, Teo A, Yeo TW. Overview of the assessment of endothelial function in humans. Front Med (Lausanne). 2020;7:542567.
21. Gallo G, Volpe M, Savoia C. Endothelial dysfunction in hypertension: Current concepts and clinical implications. Front Med (Lausanne). 2021;8:798958.
22. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.
23. VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis. Arterioscler Thromb Vac Biol. 2004;24(1):12-22.
24. Dawson LP, Lum M, Nerleker N, Nicholls S, J., Layland J. Coronary atherosclerotic plaque regression: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79(1):66-82.
25. Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. J Cell Biol. 2015;209(1):13-22.

26. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, et al. Prevalence, vascular distribution and multi-territorial extent of subclinical atherosclerosis in a middle-aged cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. Circulation. 2015;131:2104-13.
27. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: A report from the American Heart Association. Circulation. 2022;145(8):e153-e639.
28. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi S, AlKatheeri R, et al. Global epidemiology of ischemic heart disease: Results from the global burden of disease study. Cureus. 2020;12(7):e9349.
29. Australian Institute of Health and Welfare. Profile of Australia's population. Canberra: AIHW; 2023.
30. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. Int J Cardiol. 2013;168(2):934-45.
31. World Health Organization. Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2016 Geneva: World Health Organization; 2018 [Available from: https://www.who.int/healthinfo/global_burden_disease/estimates/en/.
32. Australian Institute of Health and Welfare. Cardiovascular disease snapshot 2018; Cat. no: CVD 83. Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/how-many-australians-have-cardiovascular-disease.
33. Australian Institute of Health and Welfare. Indicators of socioeconomic inequalities in cardiovascular disease, diabetes and chronic kidney disease. Canberra: AIHW; 2019.
34. Ralapanawa U, Sivakanesan R. Epidemiology and the magnitude of coronary artery disease and acute coronary syndrome: A narrative review. J Epidemiol Glob Health. 2021;11(2):169-77.
35. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results Seattle, United States: Institute for Health Metrics and Evaluation (IHME); 2020 [updated 13.07.2023. Available from: https://vizhub.healthdata.org/gbd-results/.
36. Australian Institute of Health and Welfare. Cardiovascular disease, diabetes and chronic kidney disease- Australian facts: Prevalence and incidence. Canberra: AIHW; 2014.
37. Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts: Supplementary data tables Canberra AIHW; 2023.
38. Australian Government Centre for Population. National population projections in the Intergenerational Report 2021, by broad age group, 2020-21 to 2060-61 Canberra: the Australian Government; 2021.
39. Australian Bureau of Statistics. 4821.0.55.001 Cardiovacular disease in Australia: A snapshot, 2004-2005 Canberra: Australian Bureau of Statistics; 2006 [updated 01/09/2014. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/73BBAF65CF9E6AF3CA256EB4007DE890?opendocument.
40. Villarroel M, Blackwell D, Jen A. Tables of summary health statistics for U.S. Adults: 2018 National Health Interview Survey. National Center for Health Statistics; 2019.
41. Selak V, Poppe K, Grey C, Mehta S, Winter-Smith J, Jackson R, et al. Ethnic differences in cardiovascular risk profiles among 475,241 adults in primary care in Aotearoa, New Zealand. The New Zealand Medical Journal. 2020;133(1521):14-27.
42. Australian Institute of Health and Welfare. Coronary heart disease and chronic obstructive pulmonary disease in Indigenous Australians. Canberra: AIHW; 2014.
43. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The Global Burden of Ischemic Heart Disease in 1990 and 2010: The Global Burden of Disease 2010 Study. Circulation. 2014;129(14):1493-501.
44. Australian Institute of Health and Welfare. Australian Burden of Disease Study 2022. Canberra: AIHW; 2022.
45. Australian Bureau of Statistics. Causes of Death, Australia 2022 Canberra: ABS; 2023 [Available from: https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/latest-release.
46. Australian Institute of Health and Welfare. Trends in coronary heart disease mortality: age groups and populations. Canberra: AIHW; 2014.
47. Nadlacki B, Horton D, Hossain S, Hariharaputhiran S, Ngo L, Ali A, et al. Long term survival after acute myocardial infarction in Australia and New Zealand, 2009–2015: a population cohort study. Med J Aust. 2021;214(11):519-25.

48. Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990–2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2022;8(1):50-60.
49. Munyombwe T, Hall M, Tatendashe Bernadette D, Alabas OA, Oliver G, West RM, et al. Quality of life trajectories in survivors of acute myocardial infarction: a national longitudinal study. Heart. 2020;106(1):33.
50. Australian Institute of Health and Welfare. Disease expenditure in Australia 2018-19. Canberra: AIHW; 2021.
51. Zheng H, Ehrlich F, Amin J. Productivity loss resulting from coronary heart disease in Australia. Appl Health Econ Health Policy. 2010;8(3):179-89.
52. Hyun KK, Essue BM, Woodward M, Jan S, Brieger D, Chew D, et al. The household economic burden for acute coronary syndrome survivors in Australia. BMC Health Serv Res. 2016;16(1):636.
53. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: Comparison of African American with white subjects—Atherosclerosis Risk in Communities Study. Arch Intern Med. 2007;167(6):573-9.
54. Banks E, Crouch SR, Korda RJ, Stavreski B, Page K, Thurber KA, et al. Absolute risk of cardiovascular disease events, and blood pressure- and lipid-lowering therapy in Australia. Med J Aust. 2016;204(8):320-.
55. Australian Institute of Health and Welfare. Cardiovascular disease. Canberra: AIHW; 2019.
56. Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. Am J Prev Cardiol. 2020;2:100028.
57. Alpert JS. New coronary heart disease risk factors. Am J Med. 2023;136(4):331-2.
58. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PWF, et al. Primary and subsequent coronary risk appraisal: New results from the Framingham study. Am Heart J. 2000;139(2):272-81.
59. Arnott C, Patel S, Hyett J, Jennings G, Woodward M, Celermajer DS. Women and cardiovascular disease: Pregnancy, the forgotten risk factor. Heart, Lung and Circulation. 2020;29(5):662-7.
60. Benschop L, Duvekot JJ, Jeanine ERvL. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. Heart. 2019;105(16):1273.
61. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20966 Swedish twins. J Intern Med. 2002;252(3):247-54.
62. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: The Cooper Center Longitudinal Study. Circulation. 2012;125(25):3092-8.
63. Lloyd-Jones DM, Nam B-H, D'Agostino SRB, Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adultsa prospective study of parents and offspring. JAMA. 2004;291(18):2204-11.
64. Weijmans M, van der Graaf Y, Reitsma JB, Vissern FL. Paternal or maternal history of cardiovascular disease and the risk of cardiovascular disease in offspring. A systematic review and meta-analysis. Int J Cardiol. 2015;179:409-16.
65. Kessler T, Schunkert H. Coronary artery disease genetics enlightened by genome-wide association studies. JACC: Basic to Translational Science. 2021;6(7):610-23.
66. IlL6R Genetics Consortium Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet. 2012;379(9822):1205-13.
67. Koyama S, Ito K, Terao C, Akiyama M, Horikoshi M, Momozawa Y, et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. Nat Genet. 2020;52(11):1169-77.
68. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011;57(16):1690-6.

69. Du Y-r, Liu L, Zhao Y, Huang J-j, Golden AR, Cai L. Ethnic disparities in prevalence of chronic non-communicable diseases and its multimorbidity among older adults in rural southwest China. BMC Public Health. 2023;23(1):1217.
70. Jose PO, Frank ATH, Kapphahn KI, Goldstein BA, Eggleston K, Hastings KG, et al. Cardiovascular disease mortality in Asian Americans. J Am Coll Cardiol. 2014;64(23):2486-94.
71. Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet. 2018;391(10133):1897-907.
72. Australian Bureau of Statistics. 4715.0 National Aboriginal and Torres Strait Islander Health Survey, Australia, 2018–19. Canberra; 2019.
73. Australian Bureau of Statistics. 4364055001DO001_20172018 National Health Survey: First Results, 2017–18 — Australia. Canberra; 2019.
74. Dong C, Bu X, Liu J, Wei L, Ma A, Wang T. Cardiovascular disease burden attributable to dietary risk factors from 1990 to 2019: A systematic analysis of the Global Burden of Disease study. Nutr Metab Cardiovasc Dis. 2022;32(4):897-907.
75. Biddinger KJ, Emdin CA, Haas ME, Wang M, Hindy G, Ellinor PT, et al. Association of habitual alcohol intake with risk of cardiovascular disease. JAMA Network Open. 2022;5(3):e223849-e.
76. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 2018;391(10129):1513-23.
77. Bhandari B, Liu Z, Lin S, Macniven R, Akombi-Inyang B, Hall J, et al. Long-term consumption of 10 food groups and cardiovascular mortality: A systematic review and dose response meta-analysis of prospective cohort studies. Adv Nutr. 2023;14(1):55-63.
78. Australian Institute of Health and Welfare. Australian Burden of Disease Study: Impact and causes of illness and death in Australia 2015. Canberra: AIHW; 2019.
79. World Health Organisation. Global status report on physical activity 2022. Geneva: World Health Organisation; 2022.
80. Mendis S, Puska P, Norrving B. Global atlas on cardiovascular disease prevention and control. Geneva: World Health Organization; 2011.
81. Australian Institute of Health and Welfare. Australia's health 2018. Canberra: AIHW; 2018.
82. Australian Institute of Health Welfare. Impact of physical inactivity as a risk factor for chronic conditions: Australian burden of disease. Canberra: AIHW; 2017.
83. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
84. Australian Government Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines and the Australian 24-Hour Movement Guidelines 2019 [12/04/2019:[Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines.
85. Australian Bureau of Statistics. National Health Survey, 2020-21- Australia. Table 8- Physical activity by age and sex. Canberra; 2022.
86. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob Health. 2018;6(10):e1077-e86.
87. Elgaddal N, Kramarow E, Reuben C. Physical activity among adults aged 18 and over: United States, 2020. NCHS Data Brief, no 443. Hyattsville, MD: National Center for Health Statistics; 2022.
88. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act. 2017;14(1):75.
89. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016;388(10051):1302-10.

90. Jingjie W, Yang L, Jing Y, Ran L, Yiqing X, Zhou N. Sedentary time and its association with risk of cardiovascular diseases in adults: an updated systematic review and meta-analysis of observational studies. BMC Public Health. 2022;22(1):286.
91. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. Arch Intern Med. 2012;172(6):494-500.
92. Win AM, Yen LW, Tan KH, Lim RB, Chia KS, Mueller-Riemenschneider F. Patterns of physical activity and sedentary behavior in a representative sample of a multi-ethnic South-East Asian population: a cross-sectional study. BMC Public Health. 2015;15:318.
93. Matthews CE, Carlson SA, Saint-Maurice PF, Patel S, Salerno EA, Loftfield E, et al. Sedentary behavior in U.S. adults: Fall 2019. Med Sci Sports Exerc. 2021;53(12).
94. Banks E, Joshy G, Korda RJ, Stavreski B, Soga K, Egger S, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. BMC Med 2019;17(1):128.
95. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290(7):898-904.
96. Australian Institute of Health Welfare. Biomedical risk factors Canberra: AIHW; 2022 [Available from: https://www.aihw.gov.au/reports/australias-health/biomedical-risk-factors.
97. O'Donnell C, Elosua R. Cardiovascular risk factors. Insights from Framingham Heart Study Rev Esp Cardiol. 2008;61(3):299-310.
98. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-e115.
99. Virtanen M, Vahtera J, Singh-Manoux A, Elovainio M, Ferrie JE, Kivimäki M. Unfavorable and favorable changes in modifiable risk factors and incidence of coronary heart disease: The Whitehall II cohort study. Int J Cardiol. 2018;269:7-12.
100. Rana JS, Arsenault BJ, Després J-P, Côté M, Talmud PJ, Ninio E, et al. Inflammatory biomarkers, physical activity, waist circumference, and risk of future coronary heart disease in healthy men and women. Eur Heart J. 2009;32(3):336-44.
101. Arsenault BJ, Rana JS, Stroes ESG, Després J-P, Shah PK, Kastelein JJP, et al. Beyond low-density lipoprotein cholesterol: Respective contributions of non–high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2009;55(1):35-41.
102. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. Lancet. 2020;396(10263):1644-52.
103. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J. 2017;38(32):2478-86.
104. Peters SAE, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. Atherosclerosis. 2016;248:123-31.
105. Australian Institute of Health and Welfare. Cardiovascular disease in women—a snapshot of national statistics. Canberra: AIHW; 2019.
106. Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: The Framingham experience. Arch Intern Med. 2002;162(16):1867-72.
107. Katta N, Loethen T, Lavie CJ, Alpert MA. Obesity and coronary heart disease: Epidemiology, pathology, and coronary artery imaging. Curr Probl Cardiol. 2021;46(3):100655.
108. Cai X, Li J, Cai W, Chen C, Ma J, Xie Z, et al. Meta-analysis of type 1 diabetes mellitus and risk of cardiovascular disease. J Diabetes Complications. 2021;35(4):107833.
109. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105-13.

110. Xie W, Wang Y, Xiao S, Qiu L, Yang Y, Zhang Z. Association of gestational diabetes mellitus with overall and type specific cardiovascular and cerebrovascular diseases: systematic review and meta-analysis. BMJ (Online). 2022;378.
111. Australian Institute of Health and Welfare. Diabetes: Australian facts. Canberra: AIHW; 2023.
112. Conrad N, Verbeke G, Molenberghs G, Goetschalckx L, Callender T, Cambridge G, et al. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. Lancet. 2022;400(10354):733-43.
113. Hordern MD, Dunstan D, Prins JB, Baker M, Fiatarone Singh MA, Coombes JS. Exercise prescription for patients with type 2 diabetes and pre-diabetes: A position statement from Exercise and Sport Science Australia. J Sci Med Sport. 2012;15:25-31.
114. Vinik A, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007;115:387-97.
115. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ 2010;341.
116. Pedersen SS, von Känel R, Tully PJ, Denollet J. Psychosocial perspectives in cardiovascular disease. European Journal of Preventive Cardiology. 2017;24(3_suppl):108-15.
117. Valtorta N, K. , Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart. 2016;102(13):10091016.
118. Freak-Poli R, Ryan J, Neumann JT, Tonkin A, Reid CM, Woods RL, et al. Social isolation, social support and loneliness as predictors of cardiovascular disease incidence and mortality. BMC Geriatr 2021;21(1):711.
119. Lane D, Carroll D, Lip GYH. Psychology in coronary care. QJM. 1999;92(8):425-31.
120. Golaszewski NM, LaCroix AZ, Hooker SP, Bartholomew JB. Group exercise membership is associated with forms of social support, exercise identity, and amount of physical activity. Int J Sport Exerc Psychol. 2022;20(2):630-43.
121. Stormacq C, Van den Broucke S, Wosinski J. Does health literacy mediate the relationship between socioeconomic status and health disparities? Integrative review. Health Promot Int. 2019;34(5):e1-e17.
122. Parikh PB, Yang J, Leigh S, Dorjee K, Parikh R, Sakellarios N, et al. The impact of financial barriers on access to care, quality of care and vascular morbidity among patients with diabetes and coronary heart disease. J Gen Intern Med. 2014;29(1):76-81.
123. Rozanski A. Behavioral cardiology: Current advances and future directions. J Am Coll Cardiol. 2014;64(1):100-10.
124. Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. BMC Psychiatry. 2014;14(1):371.
125. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BHM. Meta-analysis of anxiety as a risk factor for cardiovascular disease. Am J Cardiol. 2016;118(4):511-9.
126. Moryś JM, Bellwon J, Höfer S, Rynkiewicz A, Gruchała M. Quality of life in patients with coronary heart disease after myocardial infarction and with ischemic heart failure. Arch Med Sci. 2016;12(2):326-33.
127. Smaardijk VR, Maas AHEM, Lodder P, Kop WJ, Mommersteeg PMC. Sex and gender-stratified risks of psychological factors for adverse clinical outcomes in patients with ischemic heart disease: A systematic review and meta-analysis. Int J Cardiol. 2020;302:21-9.
128. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. J Am Coll Cardiol. 2023;82(9):833-955.
129. Bonnet F, Irving K, Terra J-L, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis. 2005;178(2):339-44.
130. Vancampfort D, Stubbs B, Venigalla SK, Probst M. Adopting and maintaining physical activity behaviours in people with severe mental illness: The importance of autonomous motivation. Prev Med. 2015;81:216-20.
131. Lederman O, Grainger K, Stanton R, Douglas A, Gould K, Perram A, et al. Consensus statement on the role of Accredited Exercise Physiologists within the treatment of mental disorders: a guide for mental health professionals. Australas Psychiatry. 2016;24(4):347-51.

132. Giang KW, Björck L, Novak M, Lappas G, Wilhelmsen L, Torén K, et al. Stroke and coronary heart disease: predictive power of standard risk factors into old age—long-term cumulative risk study among men in Gothenburg, Sweden. Eur Heart J. 2013;34(14):1068-74.
133. Caughey GE, Vitry AI, Gilbert AL, Roughead EE. Prevalence of comorbidity of chronic diseases in Australia. BMC Public Health. 2008;8(1):1-13.
134. Angerås O, Albertsson P, Karason K, Råmunddal T, Matejka G, James S, et al. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2013;34(5):345-53.
135. Buddeke J, Bots ML, van Dis I, Visseren FL, Hollander M, Schellevis FG, et al. Comorbidity in patients with cardiovascular disease in primary care: a cohort study with routine healthcare data. Br J Gen Pract. 2019;69(683):e398-e406.
136. Liang X, Huang Y, Han X. Associations between coronary heart disease and risk of cognitive impairment: A meta-analysis. Brain Behav. 2021;11(5):e02108.
137. Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with heart disease--United States, 2005 and 2007. MMWR Morb Mortal Wkly Rep. 2009;58(7):165-9.
138. Ball K, Crawford D, Owen N. Obesity as a barrier to physical activity. Aust N Z J Public Health. 2000;24(3):331-3.
139. Kim Y, Lai B, Mehta T, Thirumalai M, Padalabalanarayanan S, Rimmer JH, et al. Exercise training guidelines for multiple sclerosis, stroke, and parkinson disease: Rapid review and synthesis. Am J Phys Med Rehabil. 2019;98(7):613-21.
140. Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, et al. Optimal exercise programs for patients with peripheral artery disease: A scientific statement from the American Heart Association. Circulation. 2019;139(4):e10-e33.
141. O'Lone E, Kelly PJ, Masson P, Kotwal S, Gallagher M, Cass A, et al. Incidence of ischaemic heart disease in men and women with end-stage kidney disease: A cohort study. Heart Lung Circ. 2020;29(10):1517-26.
142. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. Kidney Int. 2009;76(6):652-8.
143. Baker LA, March DS, Wilkinson TJ, Billany RE, Bishop NC, Castle EM, et al. Clinical practice guideline exercise and lifestyle in chronic kidney disease. BMC Nephrol. 2022;23(1):75.
144. Rocha JA, Allison TG, Santoalha JM, Araujo V, Pereira FP, Maciel MJ. Muscoloskeletal complaints in cardiac rehabilitation: prevalence and impact on cardiovascular risk factor profile and functional and psychosocial status. Rev Port Cardiol. 2015;34(2):117-23.
145. Hinman RS, Hall M, Comensoli S, Bennell KL. Exercise & Sports Science Australia (ESSA) updated Position Statement on exercise and physical activity for people with hip/knee osteoarthritis. J Sci Med Sport. 2023;26(1):37-45.
146. Nakamura K, Fuster JJ, Walsh K. Adipokines: A link between obesity and cardiovascular disease. J Cardiol. 2014;63(4):250-9.
147. Worthley MI, Curtis MJ, Goodhart DM, Anderson TJ. Obesity is associated with impaired human coronary endothelial function. Obes Res Clin Pract. 2009;3(1):9-15.
148. Heo M, Pietrobelli A, Wang D, Heymsfield SB, Faith MS. Obesity and functional impairment: Influence of comorbidity, joint pain, and mental health. Obesity. 2010;18(10):2030-8.
149. Johnson NA, Sultana RN, Brown WJ, Bauman AE, Gill T. Physical activity in the management of obesity in adults: A position statement from Exercise and Sport Science Australia. J Sci Med Sport. 2021;24(12):1245-54.
150. Orselli MIV, Duarte M. Joint forces and torques when walking in shallow water. J Biomech. 2011;44(6):1170-5.
151. Zhu H, Jin J, Zhao G. The effects of water-based exercise on body composition: A systematic review and meta-analysis. Complement Ther Clin Pract. 2023;52:101766.
152. Javaheri AAH, Rahimi NM, Atri AE. The effects of water and land exercise programs on functional fitness factors in elderly men. Iran J Health Phys Act. 2010;1(1):1-7.

153. Kasprzak D, Kaczmarek-Majer K, Rzeźniczak J, Klamecka-Pohl K, Ganowicz-Kaatz T, Słomczyński M, et al. Cognitive impairment in cardiovascular patients after myocardial infarction: Prospective clinical study. J Clin Med. 2023;12(15):4954.
154. Moraca R, Lin E, Holmes Iv JH, Fordyce D, Campbell W, Ditkoff M, et al. Impaired baseline regional cerebral perfusion in patients referred for coronary artery bypass. J Thorac Cardiovasc Surg. 2006;131(3):540-6.
155. Anazodo UC, Shoemaker JK, Suskin N, Ssali T, Wang DJJ, St. Lawrence KS. Impaired cerebrovascular function in coronary artery disease patients and recovery following cardiac rehabilitation. Front Aging Neurosci. 2016;7(224).
156. Alosco ML, Gunstad J, Jerskey BA, Xu X, Clark US, Hassenstab J, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. Brain Behav. 2013;3(6):626-36.
157. Tomioka T, Takahashi R, Ikumi Y, Tanaka S, Ito Y, Shioiri H, et al. Influence of cognitive impairment on cardiac mortality after percutaneous coronary intervention in very elderly patients: a retrospective observational study. J Geriatr Cardiol. 2019;16(10):733-40.
158. Lautenschlager NT, Cox KL, Ellis KA. Physical activity for cognitive health: what advice can we give to older adults with subjective cognitive decline and mild cognitive impairment? Dialogues Clin Neurosci. 2019;21(1):61-8.
159. Lautenschlager N, Cox KL, Hill K, Pond D, Ellis KA, Dow B, et al. Physical activity guidelines for older Australians with mild cognitive impairment or subjective cognitive decline. Melbourne: Dementia Collaborative Research Centres; 2018.
160. Chew D, Scott IA, Cullen L, French J, Briffa T, Tideman P, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. Med J Aust. 2016;205(3):128-33.
161. National Heart Foundation of Australia. A pathway to cardiac recovery standardised program content for phase II cardiac rehabilitation. Victoria: National Heart Foundation of Australia; 2019.
162. Woodruffe S, Neubeck L, Clark RA, Gray K, Ferry C, Finan J, et al. Australian Cardiovascular Health and Rehabilitation Association (ACRA) core components of cardiovascular disease secondary prevention and cardiac rehabilitation 2014. Heart Lung Circ. 2015;24(5):430-41.
163. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(3):407-77.
164. National Institute for Health and Care Excellence. Acute coronary syndromes (NG185). UK: NICE; 2020.
165. Priel E, Wahab M, Mondal T, Freitag A, O'Byrne PM, Killian KJ, et al. The Impact of beta blockade on the cardio-respiratory system and symptoms during exercise. Curr Res Physiol. 2021;4:235-42.
166. Khan SQ, Ludman PF. Percutaneous coronary intervention. Medicine (Baltimore). 2022;50(7):437-44.
167. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
168. Cartledge S, Thomas E, Hollier K, Maddison R. Development of standardised programme content for phase II cardiac rehabilitation programmes in Australia using a modified Delphi process. BMJ Open. 2019;9(12):e032279.
169. Dibben G, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler AD, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2021;11(11):Cd001800.
170. Sumner J, Harrison A, Doherty P. The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. PLOS ONE. 2017;12(5):e0177658.
171. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf M-I, Hackbusch M, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). Eur J Prev Cardiol. 2020;27(16):1756-74.
172. Dunlay SM, Pack QR, Thomas RJ, Killian JM, Roger VL. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. Am J Med. 2014;127:538-46.

173. Francis T, Kabboul N, Rac V, Mitsakakis N, Pechlivanoglou P, Bielecki J, et al. The effect of cardiac rehabilitation on health-related quality of life in patients with coronary artery disease: A meta-analysis. Can J Cardiol. 2019;35(3):352-64.
174. Verdicchio C, Freene N, Hollings M, Maiorana A, Briffa T, Gallagher R, et al. A clinical guide for assessment and prescription of exercise and physical activity in cardiac rehabilitation. A CSANZ Position Statement. Heart Lung Circ. 2023, 32(9):1035-1048.
175. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021;28(5):460-95.
176. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021;29(1):230-45.
177. Briffa T, Maiorana A, Sheerin N, Stubbs A, Oldenburg B, Sammel N, et al. Physical activity for people with cardiovascular disease: recommendations from the National Heart Foundation of Australia. Med J Aust. 2006;184(2):71-5.
178. Briffa T, Eckermann S, Griffiths A, Harris P, Heath MR, Freedman S, et al. Cost-effectiveness of rehabilitation after an acute coronary event: a randomised controlled trial Med J Aust. 2005;183(9):450-5.
179. Driscoll A, Hinde S, Harrison A, Bojke L, Doherty P. Estimating the health loss due to poor engagement with cardiac rehabilitation in Australia. Int J Cardiol. 2020;317:7-12.
180. Norekvål TM, Bale M, Bedane HK, Hole T, Ingul CB, Munkhaugen J. Cardiac rehabilitation participation within 6 months of discharge in 37 136 myocardial infarction survivors: a nationwide registry study. Eur J Prev Cardiol. 2023:zwad350.
181. Ravn MB, Uhd M, Svendsen ML, Ørtenblad L, Maribo T. Why do patients with ischaemic heart disease drop out from cardiac rehabilitation in primary health settings. A qualitative audit of patient charts. Front Rehabil Sci. 2022;3:837174.
182. Gallagher R, Ferry C, Candelaria D, Ladak L, Zecchin R. Evaluation of cardiac rehabilitation performance and initial benchmarks for Australia: An observational cross-state and territory snapshot study. Heart Lung Circ. 2020;29(9):1397-404.
183. Astley CM, Chew DP, Keech W, Nicholls S, Beltrame J, Horsfall M, et al. The impact of cardiac rehabilitation and secondary prevention programs on 12-month clinical outcomes: A linked data analysis. Heart Lung Circ. 2020;29(3):475-82.
184. Farley RL, Wade TD, Birchmore L. Factors influencing attendance at cardiac rehabilitation among coronary heart disease patients. European Journal of Cardiovascular Nursing. 2003;2(3):205-12.
185. Taylor C, Tsakirides C, Moxon J, Moxon JW, Dudfield M, Witte K, et al. Exercise dose and all-cause mortality within extended cardiac rehabilitation: a cohort study. Open Heart. 2017;4:e000623.
186. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, et al. Systematic review of physical activity trajectories and mortality in patients with coronary artery disease. J Am Coll Cardiol. 2022;79(17):1690-700.
187. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, et al. Cardiac rehabilitation fitness changes and subsequent survival. Eur Heart J Qual Care Clin Outcomes. 2018;4(3):173-9.
188. Chen YC, Tsai JC, Liou YM, Chan P. Effectiveness of endurance exercise training in patients with coronary artery disease: A meta-analysis of randomised controlled trials. Eur J Cardiovasc Nurs. 2017;16(5):397-408.
189. Chen C-H, Chen Y-J, Tu H-P, Huang M-H, Jhong J-H, Lin K-L. Benefits of exercise training and the correlation between aerobic capacity and functional outcomes and quality of life in elderly patients with coronary artery disease. Kaohsiung J Med Sci. 2014;30(10):521-30.
190. de Bakker M, den Uijl I, ter Hoeve N, van Domburg RT, Geleijnse ML, van den Berg-Emons RJ, et al. Association between exercise capacity and health-related quality of life during and after cardiac rehabilitation in acute coronary syndrome patients: A substudy of the OPTICARE randomized controlled trial. Arch Phys Med Rehabil. 2020;101(4):650-7.
191. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Libr. 2016(1):CD001800.

192. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? Eur J Prev Cardiol. 2016;23(16):1715-33.
193. Patel H, Alkhawam H, Madanieh R, Shah N, Kosmas CE, Vittorio TJ. Aerobic vs anaerobic exercise training effects on the cardiovascular system. World J Cardiol. 2017;9(2):134-8.
194. Paluch AE, Boyer WR, Franklin BA, Laddu D, Lobelo F, Lee D-c, et al. Resistance exercise training in individuals with and without cardiovascular disease: 2023 Update: A Scientific Statement from the American Heart Association. Circulation. 2023;148.
195. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J. 2008;156(2):292-300.
196. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. Circulation. 2003;107:3152-8.
197. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000;342(7):454-60.
198. Cornelissen VA, Onkelinx S, Goetschalckx K, Thomaes T, Janssens S, Fagard R, et al. Exercise-based cardiac rehabilitation improves endothelial function assessed by flow-mediated dilation but not by pulse amplitude tonometry. Eur J Prev Cardiol. 2014;21(1):39-48.
199. Vona M, Codeluppi G, Iannino T, Ferrari E, Bogousslavsky J, von Segesser L. Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction. Circulation. 2009;119:1601-8.
200. Manresa-Rocamora A, Ribeiro F, Casanova-Lizón A, Flatt AA, Sarabia JM, Moya-Ramón M. Cardiac rehabilitation improves endothelial function in coronary artery disease patients. Int J Sports Med. 2022;43(11):905-20.
201. Hollings M, Mavros Y, Freeston J, Fiatarone Singh M. The effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. Eur J Prev Cardiol. 2017;24(12):1242-59.
202. Fan Y, Yu M, Li J, Zhang H, Liu Q, Zhao L, et al. Efficacy and safety of resistance training for coronary heart disease rehabilitation: A systematic review of randomized controlled trials. Front Cardiovasc Med. 2021;8:754794.
203. Kamiya K, Masuda T, Tanaka S, Hamazaki N, Matsue Y, Mezzani A, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. Am J Med. 2015;128(11):1212-9.
204. Momma H, Kawakami R, Honda T, Sawada SS. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. Br J Sports Med. 2022;56(13):755-63.
205. Marzolini S, Oh PI, Brooks D. Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: a meta-analysis. Eur J Prev Cardiol. 2011;19(1):81-94.
206. Volaklis K, Spassis A, Tomakadis S. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J. 2007;154:560.e1-.e6.
207. Clavario P, Barbara C, Porcile A, Russo C, Zappulla T, Capurroa E, et al. The effects of combined same session aerobic and resistance training on physical performance in coronary artery disease patients: Protocol comparison. Austin J Clin Cardiol. 2021;7(2):1077.
208. Pimenta NM, Santa-Clara H, Sardinha LB, Fernhall B. Body fat responses to a 1-year combined exercise training program in male coronary artery disease patients. Obesity. 2013;21(4):723-30.
209. Walsh J, Bilsborough W, Maiorana A, Best M, O'Driscoll G, Taylor R, et al. Exercise training improves conduit vessel function in patients with coronary artery disease. J Appl Physiol. 2003;95:20-5.
210. Dor-Haim H, Barak S, Horowitz M, Yaakobi E, Katzburg S, Swissa M, et al. Improvement in cardiac dysfunction with a novel circuit training method combining simultaneous aerobic-resistance exercises. A randomized trial. PLOS ONE. 2018;13(1):e0188551.
211. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract. 2002;56(2):115-23.

212. Maiorana A, Driscoll G, Cheetham C, Collis J, Goodman C, Rankin S, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. J Appl Physiol. 2000;88(5):1565-70.
213. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001;38(3):860-6.
214. Maiorana A, Driscoll G, Dembo L, Cheetham C, Goodman C, Taylor R, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol. 2000;279(4):H1999-H2005.
215. Alharbi M, Gallagher R, Neubeck L, Bauman A, Prebill G, Kirkness A, et al. Exercise barriers and the relationship to self-efficacy for exercise over 12 months of a lifestyle-change program for people with heart disease and/or diabetes. Eur J Cardiovasc Nurs. 2016;16(4):309-17.
216. Dibben GO, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler A-D, et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. Eur Heart J. 2023;44(6):452-69.
217. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med. 2007;356(23):2388-98.
218. Powell R, McGregor G, Ennis S, Kimani PK, Underwood M. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. BMJ Open. 2018;8(3):e019656.
219. Eijsvogels TMH, Maessen MFH, Bakker EA, Meindersma EP, van Gorp N, Pijnenburg N, et al. Association of cardiac rehabilitation with all-cause mortality among patients with cardiovascular disease in the Netherlands. JAMA Network Open. 2020;3(7):e2011686.
220. Moholdt T, Lavie CJ, Nauman J. Sustained physical activity, not weight loss, associated with improved survival in coronary heart disease. J Am Coll Cardiol. 2018;71(10):1094-101.
221. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al. Physical activity and mortality in patients with stable coronary heart disease. J Am Coll Cardiol. 2017;70(14):1689-700.
222. Marsh CE, Thomas HJ, Naylor LH, Scurrah KJ, Green DJ. Fitness and strength responses to distinct exercise modes in twins: Studies of Twin Responses to Understand Exercise as a THerapy (STRUETH) study. J Physiol. 2020;598(18):3845-58.
223. Kambic T, Šarabon N, Lainscak M, Hadžić V. Combined resistance training with aerobic training improves physical performance in patients with coronary artery disease: A secondary analysis of a randomized controlled clinical trial. Front Cardiovasc Med. 2022;9:909385.
224. Manemann SM, Chamberlain AM, Boyd CM, Miller DM, Poe KL, Cheville A, et al. Fall risk and outcomes among patients hospitalized with cardiovascular disease in the community. Circ Cardiovasc Qual Outcomes. 2018;11(8):e004199.
225. Ascencio EJ, Cieza-Gómez GD, Carrillo-Larco RM, Ortiz PJ. Timed up and go test predicts mortality in older adults in Peru: a population-based cohort study. BMC Geriatr. 2022;22(1):61.
226. Arakawa K, Ohno M, Horii M, Ishigami T, Kimura K, Tamura K. Impact of flow-mediated dilatation and coronary calcification in providing complementary information on the severity of coronary artery disease. Atherosclerosis. 2017;267:146-52.
227. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019;40(30):2534-47.
228. Agewall S, Henareh L, Kublickiene K. Endothelial function in conduit and resistance arteries in men with coronary artery disease. Atherosclerosis. 2006;184:130-6.
229. Lekakis J, Papamichael C, Vemmos C, Voutsas A, Stamatelopoulos S, Moulopoulos S. Peripheral vascular endothelial dysfunction in patients with angina pectoris and normal coronary arteriograms. J Am Coll Cardiol. 1998;31:541-6.
230. Kitta Y, Obata J-e, Nakamura T, Hirano M, Kodama Y, Fujioka D, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol. 2009;53(4):323-30.
231. Matsuzawa Y, Kwon TG, Lennon Ryan J, Lerman Lilach O, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: A systematic review and meta-analysis. J Am Heart Assoc. 2015;4(11):e002270.

232. Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular adaptation to exercise in humans: Role of Hemodynamic Stimuli. Physiol Rev. 2017;97(2):495-528.
233. Tinken T, Thijssen D, Hopkins N, Dawson E, Cable T, Green D. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension. 2010;55:312-8.
234. Tinken TM, Thijssen DHJ, Hopkins N, Black MA, Dawson EA, Minson CT, et al. Impact of shear rate modulation on vascular function in humans. Hypertension. 2009;54(2):278-85.
235. Montalvo S, Gomez M, Lozano A, Arias S, Rodriguez L, Morales-Acuna F, et al. Differences in blood flow patterns and endothelial shear stress at the carotid artery using different exercise modalities and intensities. Front Physiol. 2022;13:857816.
236. Naylor LH, Carter H, FitzSimons MG, Cable NT, Thijssen DHJ, Green DJ. Repeated increases in blood flow, independent of exercise, enhance conduit artery vasodilator function in humans. Am J Physiol Heart Circ Physiol. 2010;300(2):H664-H9.
237. Tinken TM, Thijssen DHJ, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. J Physiol. 2008;586(20):5003-12.
238. Madssen E, Moholdt T, Videm V, Wisløff U, Hegbom K, Wiseth R. Coronary atheroma regression and plaque characteristics assessed by grayscale and radiofrequency intravascular ultrasound after aerobic exercise. Am J Cardiol. 2014;114(10):1504-11.
239. Nishitani-Yokoyama M, Miyauchi K, Shimada K, Yokoyama T, Ouchi S, Aikawa T, et al. Impact of physical activity on coronary plaque volume and components in acute coronary syndrome patients after early phase II cardiac rehabilitation. Circ J. 2019;83(1):101-9.
240. Hambrecht R, Walther C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: A randomized trial. Circulation. 2004;109:1371-8.
241. Sjölin I, Bäck M, Nilsson L, Schiopu A, Leosdottir M. Association between attending exercise-based cardiac rehabilitation and cardiovascular risk factors at one-year post myocardial infarction. PLoS One. 2020;15(5):e0232772.
242. Tuesta M, Alvarez C, Pedemonte O, Araneda OF, Manríquez-Villarroel P, Berthelon P, et al. Average and interindividual effects to a comprehensive cardiovascular rehabilitation program. Int J Environ Res Public Health. 2023;20(1):261.
243. Theodorou AA, Panayiotou G, Volaklis KA, Douda HT, Paschalis V, Nikolaidis MG, et al. Aerobic, resistance and combined training and detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery disease patients. Res Sports Med. 2016;24(3):171-84.
244. Pedersen LR, Olsen RH, Anholm C, Astrup A, Eugen-Olsen J, Fenger M, et al. Effects of 1 year of exercise training versus combined exercise training and weight loss on body composition, low-grade inflammation and lipids in overweight patients with coronary artery disease: a randomized trial. Cardiovasc Diabetol. 2019;18(1):127.
245. Goldberger JJ, Subačius H, Marroquin OC, Beau SL, Simonson J. One-year landmark analysis of the effect of beta-blocker dose on survival after acute myocardial infarction. J Am Heart Assoc. 2021;10(14).
246. Carrick D, Haig C, Maznyczka AM, Carberry J, Mangion K, Ahmed N, et al. Hypertension, microvascular pathology, and prognosis after an acute myocardial infarction. Hypertension. 2018;72(3):720-30.
247. Quindry JC, McNamara M, Oser C, Fogle C. Cardiac rehabilitation and resting blood pressure: Montana Outcomes Project Cardiac Rehabilitation Registry findings. J Cardiopulm Rehabil Prev. 2022;42(2):E23-E31.
248. Baykal Sahin H, Sahin M. Effects of cardiac rehabilitation on obese hypertensive patients: A controlled trial. Hipertens Riesgo Vasc. 2023;40(4):197-204.
249. Edwards JJ, Deenmamode AHP, Griffiths M, Arnold O, Cooper N, J. , Wiles JD, et al. Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomised controlled trials. Br J Sports Med. 2023;57(20):1317.
250. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111-88.

251. Grundy S, M., Stone N, J., Bailey A, L., Beam C, Birtcher K, K., Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019;73(24):e285-e350.
252. Virani SS, Smith SC, Stone NJ, Grundy SM. Secondary prevention for atherosclerotic cardiovascular disease. Circulation. 2020;141(14):1121-3.
253. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. Egypt Heart J. 2015;67(2):89-97.
254. Sadeghi M, Khosravi-Broujeni H, Salehi-Abarghouei A, Heidari R, Masoumi G, Roohafza H. Effect of cardiac rehabilitation on inflammation: A systematic review and meta-analysis of controlled clinical trials. ARYA Atheroscler. 2018;14(2):85-94.
255. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLoS One. 2017;12(9):e0184244.
256. Anazodo UC, Shoemaker JK, Suskin N, St.Lawrence KS. An investigation of changes in regional gray mattter volume in cardiovascular disease patients, pre and post cardiovascular rehabilitation. Neuroimage Clin. 2013;3:388-95.
257. MacIntosh BJ, Swardfager W, Crane DE, Ranepura N, Saleem M, Oh PI, et al. Cardiopulmonary fitness correlates with regional cerebral grey matter perfusion and density in men with coronary artery disease. PLoS ONE. 2014;9(3):e91251.
258. Poirier SE, Suskin NG, Khaw AV, Thiessen JD, Shoemaker JK, Anazodo UC. Probing evidence of cerebral white matter microstructural disruptions in ischemic heart disease before and following cardiac rehabilitation: A diffusion tensor MR imaging study. J Magn Reson Imaging. 2023 (ePub).
259. Coombs GB, Al-Khazraji BK, Suskin N, Shoemaker JK. Impact of ischemic heart disease and cardiac rehabilitation on cerebrovascular compliance. J Appl Physiol (1985). 2023;135(4):753-62.
260. Valaikiene J, Ryliskyte L, Valaika A, Puronaite R, Dementaviciene J, Vaitkevicius A, et al. A high prevalence of intracranial stenosis in patients with coronary artery disease and the diagnostic value of Transcranial Duplex Sonography. J Stroke Cerebrovasc Dis. 2019;28(4):1015-21.
261. Perdomo SJ, Ward J, Liu Y, Vidoni ED, Sisante JF, Kirkendoll K, et al. Cardiovascular disease risk is associated with middle cerebral artery blood flow velocity in older adults. Cardiopulm Phys Ther J. 2020;31(2):38-46.
262. Xiao Z, Ren X, Zhao Q, Wu W, Liang X, Tang J, et al. Relation of middle cerebral artery flow velocity and risk of cognitive decline: A prospective community-based study. J Clin Neurosci. 2022;97:56-61.
263. Smith PJ, Browndyke JN, Monge ZA, Harshbarger TB, James ML, Gaca JG, et al. Longitudinal changes in regional cerebral perfusion and cognition after cardiac operation. Ann Thorac Surg. 2019;107(1):112-8.
264. Santiago C, Herrmann N, Swardfager W, Saleem M, Oh PI, Black SE, et al. White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. Am J Geriatr Psychiatry. 2015;23(7):754-63.
265. Stanek KM, Gunstad J, Spitznagel MB, Waechter D, Hughes JW, Luyster F, et al. Improvements in cognitive function following cardiac rehabilitation for older adults with cardiovascular disease. Int J Neurosci. 2011;121(2):86-93.
266. Hoiland RL, Caldwell HG, Howe CA, Nowak-Flück D, Stacey BS, Bailey DM, et al. Nitric oxide is fundamental to neurovascular coupling in humans. J Physiol. 2020;598(21):4927-39.
267. Hoiland RL, Caldwell HG, Carr JMJR, Howe CA, Stacey BS, Dawkins T, et al. Nitric oxide contributes to cerebrovascular shear-mediated dilatation but not steady-state cerebrovascular reactivity to carbon dioxide. J Physiol. 2022;600(6):1385-403.
268. Saleem M, Herrmann N, Dinoff A, Mazereeuw G, Oh PI, Goldstein BI, et al. Association between endothelial function and cognitive performance in patients with coronary artery disease during cardiac rehabilitation. Psychosom Med. 2019;81(2):184-91.
269. Alsaleh E, Baniyasin F. Prevalence of physical activity levels and perceived benefits of and barriers to physical activity among Jordanian patients with coronary heart disease: A cross-sectional study. Front Public Health. 2022;10:1041428.
270. Huang W-T, Liu C-Y, Hung H-F, Hsu S-P, Chiou A-F. Gender differences in factors associated with physical activity in patients with coronary artery disease. J Cardiovasc Nurs. 2022;37(4):386-77.

271. Griffo R, Ambrosetti M, Tramarin R, Fattirolli F, Temporelli PL, Vestri AR, et al. Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey. Int J Cardiol. 2012,167(4):1390-5.
272. Reid RD, Morrin LI, Pipe AL, Dafoe WA, Higginson LAJ, Wielgosz AT, et al. Determinants of physical activity after hospitalization for coronary artery disease: the Tracking Exercise After Cardiac Hospitalization (TEACH) Study. Eur J Cardiovasc Prev Rehabil. 2006;13(4):529-37.
273. Tang LH, Doherty P, Skou ST, Harrison A. Optimal outcomes from cardiac rehabilitation are associated with longer-term follow-up and risk factor status at 12 months: An observational registry-based study. Int J Cardiol. 2023;386:134-40.
274. Fell J, Dale V, Doherty P. Does the timing of cardiac rehabilitation impact fitness outcomes? An observational analysis. Open Heart. 2016;3(1):e000369.
275. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019;26(8):824-35.
276. Guiraud T, Granger R, Bousquet V, Richard M, Soukarie L, Babin L, et al. Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program. Ann Phys Rehabil Med. 2012;55(5):312-21.
277. Marzolini S, Candelaria H, Oh P. Prevalence and impact of musculoskeletal comorbidities in cardiac rehabilitation. J Cardiopulm Rehabil Prev. 2010;30(6):391-400.
278. LaPier TK, Cleary K, Kidd J. Exercise self-efficacy, habitual physical activity, and fear of falling in patients with coronary heart disease. Cardiopulm Phys Ther J. 2009;20(4):5-11.
279. Marzolini S, Brooks D, Oh PI. Sex differences in completion of a 12-month cardiac rehabilitation programme: an analysis of 5922 women and men. Eur J Cardiovasc Prev Rehabil. 2008;15(6):698-703.
280. Resurrección DM, Moreno-Peral P, Gómez-Herranz M, Rubio-Valera M, Pastor L, Caldas de Almeida JM, et al. Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. Eur J Cardiovasc Nurs. 2019;18(1):38-47.
281. Borg S, Öberg B, Leosdottir M, Lindolm D, Nilsson L, Bäck M. Factors associated with non-attendance at exercise-based cardiac rehabilitation. BMC Sports Sci Med Rehabil. 2019;11(1):13.
282. Slovinec D'Angelo ME, Pelletier LG, Reid RD, Huta V. The roles of self-efficacy and motivation in the prediction of short- and long-term adherence to exercise among patients with coronary heart disease. Health Psychol. 2014;33(11):1344-53.
283. Blanchard CM, Reid RD, Morrin LI, Beaton LJ, Pipe A, Courneya KS, et al. Barrier self-efficacy and physical activity over a 12-month period in men and women who do and do not attend cardiac rehabilitation. Rehabil Psychol. 2007;52(1):65-73.
284. Collado-Mateo D, Lavín-Pérez AM, Peñacoba C, Del Coso J, Leyton-Román M, Luque-Casado A, et al. Key factors associated with adherence to physical exercise in patients with chronic diseases and older adults: An umbrella review. Int J Environ Res Public Health. 2021;18(4):2023.
285. Dorn J, Naughton J, Imamura DAI, Trevisan M. Correlates of compliance in a randomized exercise trial in myocardial infarction patients. Med Sci Sports Exerc. 2001;33(7):1081-9.
286. Petter M, Blanchard C, Kemp KAR, Mazoff AS, Ferrier SN. Correlates of exercise among coronary heart disease patients: review, implications and future directions. Eur J Cardiovasc Prev Rehabil. 2009;16(5):515-26.
287. Bourke R, Doody P, Pérez S, Moloney D, Lipsitz LA, Kenny RA. Cardiovascular disorders and falls among older adults: A systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2024;79(2):1-15.
288. Papalia GF, Papalia R, Diaz Balzani LA, Torre G, Zampogna B, Vasta S, et al. The effects of physical exercise on balance and prevention of falls in older people: A systematic review and meta-analysis. J Clin Med. 2020;9(8):2595.
289. Denfeld QE, Turrise S, MacLaughlin EJ, Chang P-S, Clair WK, Lewis EF, et al. Preventing and managing falls in adults with cardiovascular disease: A Scientific Statement from the American Heart Association. Circ Cardiovasc Qual Outcomes. 2022;15(6):e000108.

290. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020;72(2):220-33.
291. Becker B. Aquatic therapy: Scientific foundations and clinical rehabilitation applications Am J Phys Med Rehabil. 2009;1(9):859-72.
292. Torres-Ronda L, Del Alcázar XSI. The properties of water and their applications for training. J Hum Kinet 2014;44:237-48.
293. Wilcock IM, Cronin JB, Hing WA. Physiological response to water immersion. Sports Med. 2006;36(9):747-65.
294. Speight JG. Rules of Thumb for Petroleum Engineers. New York: New York: John Wiley & Sons, Incorporated; 2017.
295. The Editors of Encyclopedia Britannica. Archimedes' Principle. In: The Editors of Encyclopedia, editor. Encyclopedia Britannica: Encyclopedia Britannica, Inc.; 2020.
296. International Towing Tank Conference. ITTC quality system manual recommended procedures and guidelines: Fresh water and seawater properties. 2011.
297. Adegoke BOA, Bello AI, Abass AO. Variation in percentage weight bearing with changes in standing posture during water immersion: implication for clinical practice. BMC Musculoskel Disord. 2014;15:261.
298. Carter HH, Cheng JL, MacDonald MJ, Pienaar O, Coleman A, Naylor LH, et al. The effects of exercise during water immersion on arterial function in humans. Am J Physiol Regul Integr Comp Physiol. 2023;324(4):R568-R73.
299. Carter HH, Spence AL, Ainslie PN, Pugh CJA, Naylor LH, Green DJ. Differential impact of water immersion on arterial blood flow and shear stress in the carotid and brachial arteries of humans. Physiol Rep. 2017;5(10):e13285-e.
300. Carter HH, Pienaar O, Coleman A, Cheng JL, MacDonald MJ, Naylor LH, et al. The effects of water temperature on cerebral blood flow during aquatic exercise. Eur J Appl Physiol. 2024, 124(1):219-225.
301. Pöyhönen T, Keskinen KL, Hautala A, Mälkiä E. Determination of hydrodynamic drag forces and drag coefficients on human leg/foot model during knee exercise. Clin Biomech. 2000;15(4):256-60.
302. Visconti G, Ruggieri P. Fluid Dynamics: Fundamentals and Applications: Springer; 2020.
303. Tu J, Yeoh GH, Liu C. Computational Fluid Dynamics: A Practical Approach. Saint Louis: Saint Louis: Elsevier Science & Technology; 2018.
304. Craig Jr AB, Dvorak M. Thermal regulation during water immersion. J Appl Physiol. 1966;21(5):1577-85.
305. Park KS, Choi JK, Park YS. Cardiovascular regulation during water immersion. Appl Human Sci. 1999;18(6):233-41.
306. Yun SH, Choi JK, Park YS. Cardiovascular responses to head-out water immersion in Korean women breath-hold divers. Eur J Appl Physiol. 2004;91(5-6):708-11.
307. Kollias J, Barlett L, Bergsteinova V, Skinner JS, Buskirk ER, Nicholas WC. Metabolic and thermal responses of women during cooling in water. J Appl Physiol. 1974;36(5):577-80.
308. McArdle WD, Magel JR, Gergley TJ, Spina RJ, Toner MM. Thermal adjustment to cold-water exposure in resting men and women. J Appl Physiol. 1984;56(6):1565-71.
309. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: Sex and race differences. Obesity. 2011;19(2):402-8.
310. Movsesyan L, Tankó LB, Larsen PJ, Christiansen C, Svendsen OL. Variations in percentage of body fat within different BMI groups in young, middle-aged and old women. Clin Physiol Funct Imaging. 2003;23(3):130-3.
311. Chambers AJ, Sukits AL, McCrory JL, Cham R. The effect of obesity and gender on body segment parameters in older adults. Clin Biomech. 2010;25(2):131-6.
312. DeGroot DW, Havenith G, Kenney WL. Responses to mild cold stress are predicted by different individual characteristics in young and older subjects. J Appl Physiol. 2006;101(6):1607-15.
313. Ayme K, Gavarry O, Rossi P, Desruelle A-V, Regnard J, Boussuges A. Effect of head-out water immersion on vascular function in healthy subjects. Appl Physiol Nutr Metab. 2014;39(4):425-31.
314. Gauer O. Recent advances in the physiology of whole body immersion. Acta Astronaut. 1975;2:31-9.

315. Herring N, Paterson DJ. Levick's Introduction to Cardiovascular Physiology. Milton, United Kingdom: Taylor & Francis Group; 2018.
316. Carter HH, Spence AL, Pugh CJ, Ainslie P, Naylor LH, Green DJ. Cardiovascular responses to water immersion in humans: impact on cerebral perfusion. Am J Physiol Regul Integr Comp Physiol. 2014;306:R636-R40.
317. Mano T, Iwase S, Saito M, Koga I, Abe H, Inamura K, et al. Neural and humoral controlling mechanisms of cardiovascular functions in man under weightlessness simulated by water immersion. Acta Astronaut. 1991;23:31-3.
318. Gabrielsen A, Warberg J, Christensen N, Bie P, Stadeager C, Pump B, et al. Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am J Physiol Regul Integr Comp Physiol. 2000;278:1583-8.
319. Cider A, Sveälv BG, Täng MS, Schaufelberger M, Andersson B. Immersion in warm water induces improvement in cardiac function in patients with chronic heart failure. Eur J Heart Fail. 2006;8(3):308-13.
320. Johansen LB, Pump B, Warberg J, Christensen NJ, Norsk P. Preventing hemodilution abolishes natriuresis of water immersion in humans. Am J Physiol Regul Integr Comp Physiol. 1998;275(3):R879-R88.
321. Kinney EL, Cortada X, Ventura R. Cardiac size and motion during water immersion: Implications for volume homeostasis. Am Heart J. 1987;113(2, Part 1):345-9.
322. Gabrielsen, VidebÆk, Johansen, Warberg, Christensen, Pump, et al. Forearm vascular and neuroendocrine responses to graded water immersion in humans. Acta Physiol Scand. 2000;169(2):87-94.
323. Gabrielsen A, Sørensen VB, Pump B, Galatius S, Videbæk R, Bie P, et al. Cardiovascular and neuroendocrine responses to water immersion in compensated heart failure. Am J Physiol Heart Circ Physiol. 2000;279(4):H1931-H40.
324. Christie J, Sheldahl L, Tristani F, Wann L, Sagar K, Levandoski S, et al. Cardiovascular regulation during head- out water immersion exercise. J Appl Physiol. 1990;69:657-64.
325. Mourot L, Bouhaddi M, Gandelin E, Cappelle S, Dumoulin G, Wolf J-P, et al. Cardiovascular autonomic control during short-term thermoneutral and cool head-out immersion. Aviat Space Environ Med. 2008;79(1):14-20.
326. Itoh M, Fukuoka Y, Kojima S, Araki H, Hotta N, Sakamoto T, et al. Comparison of cardiovascular autonomic responses in elderly and young males during head-out water immersion. J Cardiol. 2007;49(5):241-50.
327. Farhi LE, Linnarsson D. Cardiopulmonary readjustments during graded immersion in water at 35 °C. Respir Physiol. 1977;30(1–2):35-50.
328. Derion T, Guy HJ, Tsukimoto K, Schaffartzik W, Prediletto R, Poole DC, et al. Ventilation-perfusion relationships in the lung during head-out water immersion. J Appl Physiol. 1992;72(1):64-72.
329. Stadeager C, Johansen LB, Warberg J, Christensen NJ, Foldager N, Bie P, et al. Circulation, kidney function, and volume-regulating hormones during prolonged water immersion in humans. J Appl Physiol (1985). 1992;73(2):530.
330. Choukroun ML, Varene P. Adjustments in oxygen transport during head-out immersion in water at different temperatures. J Appl Physiol. 1990;68(4):1475-80.
331. Boussuges A. Immersion in thermoneutral water: Effects on arterial compliance. Aviat Space Environ Med. 2006;77:1183-7.
332. Bréchat PH, Wolf JP, Simon-Rigaud ML, Bréchat N, Kantelip JP, Regnard J. Hemodynamic requirements and thoracic fluid balance during and after 30 minutes immersed exercise: Caution in immersion rehabilitation programmes. Sci Sports. 2013;28(1):17-28.
333. Shiraishi M, Schou M, Gybel M, Christensen NJ, Norsk P. Comparison of acute cardiovascular responses to water immersion and head-down tilt in humans. J Appl Physiol. 2002;92(1):264-8.
334. Magnusson G, Kaijser L, Sylvén C, Karlberg K-E, Isberg B, Saltin B. Peak skeletal muscle perfusion is maintained in patients with chronic heart failure when only a small muscle mass is exercised. Cardiovasc Res. 1997;33(2):297-306.
335. Schega L, Claus G, Almeling M, Niklas A, Daly D. Cardiovascular responses during thermoneutral, head-out water immersion in patients with coronary artery disease. J Cardiopulm Rehabil. 2007;27:76-80.

336. Grüner Sveälv B, Cider A, Täng MS, Angwald E, Kardassis D, Andersson B. Benefit of warm water immersion on biventricular function in patients with chronic heart failure. Cardiovasc Ultrasound. 2009;7:33.
337. Shah P, Pellicori P, Kallvikbacka-Bennett A, Zhang J, Pan D, Clark AL. Warm water immersion in patients with chronic heart failure: a pilot study. Clin Res Cardiol. 2019;108(5):468-76.
338. Schmid J-P, Morger C, Noveanu M, Binder RK, Anderegg M, Saner H. Haemodynamic and arrhythmic effects of moderately cold (22°C) water immersion and swimming in patients with stable coronary artery disease and heart failure. Eur J Heart Fail. 2009;11(9):903-9.
339. Schmid JP, Noveanu M, Morger C, Gaillet R, Capoferri M, Anderegg M, et al. Influence of water immersion, water gymnastics and swimming on cardiac output in patients with heart failure. Heart. 2007;93(6):722-7.
340. Meyer K, Bücking J. Exercise in heart failure: should aqua therapy and swimming be allowed? Med Sci Sports Exerc. 2004;36(12):2017-23.
341. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Exercise rehabilitation restores physiological cardiovascular responses to short-term head-out water immersion in patients with chronic heart failure. J Cardiopulm Rehabil Prev. 2010;30(1):22-7.
342. Pugsley J, Lerner AB. Cardiac output monitoring: Is there a gold standard and how do the newer technologies compare? Semin Cardiothorac Vasc Anesth. 2010;14(4):274-82.
343. Kim GE, Kim SY, Kim SJ, Yun SY, Jung HH, Kang YS, et al. Accuracy and efficacy of impedance cardiography as a non-invasive cardiac function monitor. Yonsei Med J. 2019;60(8):735-41.
344. O'Leary DD, Kimmerly DS, Cechetto AD, Shoemaker JK. Differential effect of head-up tilt on cardiovagal and sympathetic baroreflex sensitivity in humans. Exp Physiol. 2003;88(6):769-74.
345. Muller MD, Kim C-H, Seo Y, Ryan EJ, Glickman EL. Hemodynamic and thermoregulatory responses to lower body water immersion. Aviat Space Environ Med. 2012;83(10):935-41.
346. LaMarca B, Alexander BT. Sex differences in cardiovascular physiology and pathophysiology. San Diego, United States: Elsevier Science & Technology; 2019.
347. Nakamitsu S, Sagawa S, Miki K, Wada F, Nagaya K, Keil LC, et al. Effect of water temperature on diuresis-natriuresis: AVP, ANP, and urodilatin during immersion in men. J Appl Physiol. 1994;77(4):1919-25.
348. Gabrielsen A, Bie P, Holstein-Rathlou NH, Christensen NJ, Warberg J, Dige-Petersen H, et al. Neuroendocrine and renal effects of intravascular volume expansion in compensated heart failure. Am J Physiol Regul Integr Comp Physiol. 2001;281(2):R459-R67.
349. Ogihara T, Shima J, Hara H, Tabuchi Y, Hashizume K, Nagano M, et al. Significant increase in plasma immunoreactive atrial natriuretic polypeptide concentration during head-out water immersion. Life Sci. 1986;38(26):2413-8.
350. Johansen LB, Jensen TUS, Pump B, Norsk P. Contribution of abdomen and legs to central blood volume expansion in humans during immersion. Journal of Applied Physiology. 1997;83(3):695-9.
351. Hildenbrand KJ, Becker BE, Whitcomb R, Sanders JP. Age-dependent autonomic changes following immersion in cool, neutral, and warm water temperatures. Int J Aquat Res. 2010;4:4.
352. Risch WD, Koubenec HJ, Beckmann U, Lange S, Gauer OH. The effect of graded immersion on heart volume, central venous pressure, pulmonary blood distribution, and heart rate in man. Pflugers Arch. 1978;374(2):115-8.
353. Kruel LF, Peyre-Tartaruga LA, Coertjens M, Dias AB, Da Silva RC, Rangel AC. Using heart rate to prescribe physical exercise during head-out water immersion. J Strength Cond Res. 2014;28(1):281-9.
354. Šrámek P, Šimečková M, Janský L, Šavlíková J, Vybíral S. Human physiological responses to immersion into water of different temperatures. Eur J Appl Physiol Occup Physiol. 2000;81(5):436-42.
355. Worley ML, Reed EL, P JK, Dirr J, Klaes N, Schlader ZJ, et al. Hot head-out water immersion does not acutely alter dynamic cerebral autoregulation or cerebrovascular reactivity to hypercapnia. Temperature (Austin). 2021;8(4):381-401.
356. Crandall CG, González-Alonso J. Cardiovascular function in the heat-stressed human. Acta Physiol (Oxf). 2010;199(4):407-23.
357. Johansen LB, Bie P, Warberg J, Christensen NJ, Norsk P. Role of hemodilution on renal responses to water immersion in humans. Am J Physiol. 1995, 269(5 Pt 2):R1068-76.

358. Fahri L, Linnarsson D. Cardiopulmonary readjustments during graded immersion in water at 35ºC. Respir Physiol. 1977;30:35-50.
359. Dionne A, Leone M, Goulet S, Andrich DE, Pérusse L, Comtois A-S. Acute effects of water immersion on heart rate variability in participants with heart disease. Clin Physiol Funct Imaging. 2018;38(2):233-9.
360. Alba BK, Castellani JW, Charkoudian N. Cold-induced cutaneous vasoconstriction in humans: Function, dysfunction and the distinctly counterproductive. Exp Physiol. 2019;104(8):1202-14.
361. Pugh CJ, Sprung VS, Ono K, Spence AL, Thijssen DHJ, Carter HH, et al. The effect of water immersion during exercise on cerebral blood flow. Med Sci Sports Exerc. 2015;47(2):299-306.
362. Ueno LM, Miyachi M, Matsui T, Takahashi K, Yamazaki K, Hayashi K, et al. Effect of aging on carotid artery stiffness and baroreflex sensitivity during head-out water immersion in man. Braz J Med Biol Res. 2005;38:629-37.
363. Risch WD, Koubenec H-J, Gauer OH, Lange S. Time course of cardiac distension with rapid immersion in a thermo-neutral bath. Pflügers Archiv. 1978;374(2):119-20.
364. Ballermann BJ, Dardik A, Eng E, Liu A. Shear stress and the endothelium. Kidney Int 1998;54:S100-S8.
365. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc. 2009;84(9):822-30.
366. Bailey TG, Cable NT, Miller GD, Sprung VS, Low DA, Jones H. Repeated warm water immersion induces similar cerebrovascular adaptations to 8 weeks of moderate-intensity exercise training in females. Int J Sports Med. 2016;37(10):757-65.
367. Herrington DM, Kesler K, Reiber JHC, Davis W, Brown WV, Helms R, et al. Arterial compliance adds to conventional risk factors for prediction of angiographic coronary artery disease. Am Heart J. 2003;146(4):662-7.
368. Greaney JL, Kenney WL, Alexander LM. Neurovascular mechanisms underlying augmented cold-induced reflex cutaneous vasoconstriction in human hypertension. J Physiol. 2017;595(5):1687-98.
369. Sato D, Onishi H, Yamashiro K, Iwabe T, Shimoyama Y, Maruyama A. Water immersion to the femur level affects cerebral cortical activity in humans: Functional near-infrared spectroscopy study. Brain Topogr. 2012;25(2):220-7.
370. Ainslie PN, Duffin J. Integration of cerebrovascular CO2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. Am J Physiol Regul Integr Comp Physiol. 2009;296(5):R1473-R95.
371. Sackett JR, Schlader ZJ, Cruz C, Hostler D, Johnson BD. The effect of water immersion and acute hypercapnia on ventilatory sensitivity and cerebrovascular reactivity. Physiol Rep. 2018;6(20):e13901.
372. Miyazawa T, Horiuchi M, Komine H, Sugawara J, Fadel PJ, Ogoh S. Skin blood flow influences cerebral oxygenation measured by near-infrared spectroscopy during dynamic exercise. Eur J Appl Physiol. 2013;113(11):2841-8.
373. Leal JC, Mateus SRM, Horan TA, Beraldo PSS. Effect of graded water immersion on vital capacity and plasma volume in patients with cervical spinal cord injury. Spinal Cord. 2010;48(5):375-9.
374. de Andrade AD, Júnior JC, Lins de Barros Melo TL, Rattes Lima CSF, Brandão DC, Melo Barcelar J. Influence of different levels of immersion in water on the pulmonary function and respiratory muscle pressure in healthy individuals: Observational study. Physiother Res Int. 2014;19(3):140-6.
375. Craig AB, Dvorak M. Expiratory reserve volume and vital capacity of the lungs during immersion in water. J Appl Physiol. 1975;38(1):5-9.
376. Hoshi D, Fukuie M, Tamai S, Momma R, Tarumi T, Sugawara J, et al. Influence of water immersion on the airway impedance measured by forced oscillation technique. Respir Physiol Neurobiol. 2022;295:103779.
377. Prefaut C, Lupi-h E, Anthonisen NR. Human lung mechanics during water immersion. J Appl Physiol. 1976;40(3):320-3.
378. Begin R, Epstein M, Sackner MA, Levinson R, Dougherty R, Duncan D. Effects of water immersion to the neck on pulmonary circulation and tissue volume in man. J Appl Physiol. 1976;40(3):293-9.
379. Hong SK, Cerretelli P, Cruz JC, Rahn H. Mechanics of respiration during submersion in water. J Appl Physiol. 1969;27(4):535-8.
380. Smith JR, Taylor BJ. Inspiratory muscle weakness in cardiovascular diseases: Implications for cardiac rehabilitation. Prog Cardiovasc Dis. 2022;70:49-57.

381. McNamara R, J. , McKeough Z, J., McKenzie D, K. , Alison J, A. . Water-based exercise in COPD with physical comorbidities: a randomised controlled trial. Eur Respir J. 2013;41(6):1284.
382. Yamashina Y, Yokoyama H, Naghavi N, Hirasawa Y, Takeda R, Ota A, et al. Treadmill walking in water induces greater respiratory muscle fatigue than treadmill walking on land in healthy young men. J Physiol Sci. 2016;66(3):257-64.
383. Harrison R, Bulstrode S. Percentage weight-bearing during partial immersion in the hydrotherapy pool. Physiother Pract. 1987;3(2):60-3.
384. Abdalbary SA. Partial weight bearing in hip fracture rehabilitation. Future Sci OA. 2018;4(1):Fso254.
385. Madeira F, Brito RNd, Emer AA, Batisti AP, Turnes BL, Salgado ASI, et al. The role of spinal inhibitory neuroreceptors in the antihyperalgesic effect of warm water immersion therapy. Braz J Phys Ther. 2021;25(1):56-61.
386. Martins DF, Brito RN, Stramosk J, Batisti AP, Madeira F, Turnes BL, et al. Peripheral neurobiologic mechanisms of antiallodynic effect of warm water immersion therapy on persistent inflammatory pain. J Neurosci Res. 2015;93(1):157-66.
387. Bressel E, Louder TJ, Raikes AC, Alphonsa S, Kyvelidou A. Water immersion affects episodic memory and postural control in healthy older adults. J Geriatr Phys Ther. 2019;42(4):E1-E6.
388. Schaefer SY, Louder TJ, Foster S, Bressel E. Effect of water immersion on dual-task performance: Implications for aquatic therapy. Physiother Res Int. 2016;21(3):147-54.
389. Becker B, Hildenbrand K, Whitcomb RK, Sanders JP. Biophysiologic effects of warm water immersion. Int J Aquat Res Educ. 2009;3:24-37.
390. Joho S. Muscle sympathetic nerve activity and cardiovascular disease. In: Iwase S, Hayano J, Orimo S, editors. Clinical Assessment of the Autonomic Nervous System. Tokyo: Springer Japan; 2017. p. 31-46.
391. Sato D, Yamazaki Y, Takahashi A, Uetake Y, Nakano S, Iguchi K, et al. Water immersion decreases sympathetic skin response during color–word Stroop test. PLoS ONE. 2017;12(7):e0180765.
392. Chen Y, Yu Y, Zou W, Zhang M, Wang Y, Gu Y. Association between cardiac autonomic nervous dysfunction and the severity of coronary lesions in patients with stable coronary artery disease. J Int Med Res. 2018;46(9):3729-40.
393. Vuoti AO, Tulppo MP, Ukkola OH, Junttila MJ, Huikuri HV, Kiviniemi AM, et al. Prognostic value of heart rate variability in patients with coronary artery disease in the current treatment era. PLoS ONE. 2021;16(7):1.
394. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health. 2017;5:258.
395. Malik M, Bigger JT, Camm AJ, Kleiger RE, Malliani A, Moss AJ, et al. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Eur Heart J. 1996;17(3):354-81.
396. Chouchou F, Pichot V, Costes F, Guillot M, Barthélémy J-C, Bertoletti L, et al. Autonomic cardiovascular adaptations to acute head-out water immersion, head-down tilt and supine position. Eur J Appl Physiol. 2020;120(2):337-47.
397. Leyk D, Essfeld D, Hoffmann U, Wunderlich HG, Baum K, Stegemann J. Postural effect on cardiac output, oxygen uptake and lactate during cycle exercise of varying intensity. Eur J Appl Physiol Occup Physiol. 1994;68(1):30-5.
398. Besnier F, Labrunée M, Pathak A, Pavy-Le Traon A, Galès C, Sénard J-M, et al. Exercise training-induced modification in autonomic nervous system: An update for cardiac patients. Ann Phys Rehabil Med. 2017;60(1):27-35.
399. Goldberger JJ, Arora R, Buckley U, Shivkumar K. Autonomic nervous system dysfunction: JACC Focus Seminar. J Am Coll Cardiol. 2019;73(10):1189-206.
400. Dekker Jacqueline M, Crow Richard S, Folsom Aaron R, Hannan Peter J, Liao D, Swenne Cees A, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. Circulation. 2000;102(11):1239-44.
401. Craig A, Dvorak M. Thermal regulation of man exercising during water immersion. J Appl Physiol. 1968;25:28-35.
402. Looney DP, Long ET, Potter AW, Xu X, Friedl KE, Hoyt RW, et al. Divers risk accelerated fatigue and core temperature rise during fully-immersed exercise in warmer water temperature extremes. Temperature (Austin). 2019;6(2):150-7.

403. Israel DJ, Heydon KM, Edlich RF, Pozos RS, Wittmers LE, Jr. Core temperature response to immersed bicycle ergometer exercise at water temperatures of 21 degrees, 25 degrees, and 29 degrees C. J Burn Care Rehabil. 1989;10(4):336-45.
404. Sheldahl LM, Tristani FE, Clifford PS, Hughes CV, Sobocinski KA, Morris RD. Effect of head-out water immersion on cardiorespiratory response to dynamic exercise. J Am Coll Cardiol. 1987;10(6):1254-8.
405. Hanna RD, Sheldahl LM, Tristani FE. Effect of enhanced preload with head-out water immersion on exercise response in men with healed myocardial infarction. Am J Cardiol. 1993;71(12):1041-4.
406. McMurray RG, Fieselman CC, Avery KE, Sheps DS. Exercise hemodynamics in water and on land in patients with coronary artery disease. J Cardpulm Rehabil. 1988;8(2):69-75.
407. Cider Å, Schaufelberger M, Andersson B, Sunnerhagen KS. Cardiorespiratory effects of warm water immersion in elderly patients with chronic heart failure. Clin Physiol Funct Imaging. 2005;25(6):313-7.
408. Ayme K, Gavarry O, Rossi P, Guieu R, Boussuges A. Changes in cardio-vascular function after a single bout of exercise performed on land or in water: A comparative study. Int J Cardiol. 2014;176(3):1377-8.
409. Joubert DP, Granados JZ, Oliver JM, Noack BL, Grandjean PW, Woodman CR, et al. An acute bout of aquatic treadmill exercise induces greater improvements in endothelial function and postexercise hypotension than land treadmill exercise: A crossover study. Am J Phys Med Rehabil. 2018;97(8).
410. Hashimoto Y, Okamoto T. Acute effects of walking in water on vascular endothelial function and heart rate variability in healthy young men. Clin Exp Hypertens. 2019;41(5):452-9.
411. Thijssen D, Dawson E, Tinken T, Cable N, D. G. Retrograde flow and shear rate acutely impair endothelial function in humans. Hypertension. 2009;53(6):986-92.
412. Schreuder THA, Green DJ, Hopman MTE, Thijssen DHJ. Impact of retrograde shear rate on brachial and superficial femoral artery flow-mediated dilation in older subjects. Atherosclerosis. 2015;241(0):199-204.
413. Cheng JL, Au JS, MacDonald MJ. Peripheral artery endothelial function responses to altered shear stress patterns in humans. Exp Physiol. 2019;104(7):1126-35.
414. Atkinson CL, Lewis NCS, Carter HH, Thijssen DHJ, Ainslie PN, Green DJ. Impact of sympathetic nervous system activity on post-exercise flow-mediated dilatation in humans. J Physiol. 2015;593(23):5145-56.
415. Parfitt R, Hensman MY, Lucas SJE. Cerebral blood flow responses to aquatic treadmill exercise. Med Sci Sports Exerc. 2017;49(7):1305-1312.
416. Gayda M, Gremeaux V, Bherer L, Juneau M, Drigny J, Dupuy O, et al. Cognitive function in patients with stable coronary heart disease: Related cerebrovascular and cardiovascular responses. PLoS One. 2017;12(9):e0183791.
417. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Endothelial dysfunction, increased arterial stiffness, and cardiovascular risk prediction in patients with coronary artery disease: FMD-J (Flow-Mediated Dilation Japan) Study A. J Am Heart Assoc. 2018;7(14):e008588.
418. Colado JC, Borreani S, Pinto SS, Tella V, Martin F, Flandez J, et al. Neuromuscular responses during aquatic resistance exercise with different devices and depths. J Strength Cond Res. 2013;27(12):3384-90.
419. Borreani S, Colado JC, Furio J, Martin F, Tella V. Muscle activation in young men during a lower limb aquatic resistance exercise with different devices. Phys Sportsmed. 2014;42(2):80-7.
420. Psycharakis SG, Coleman SGS, Linton L, Kaliarntas K, Valentin S. Muscle activity during aquatic and land exercises in people with and without low back pain. Phys Ther. 2019;99(3):297-310.
421. Psycharakis SG, Coleman SGS, Linton L, Valentin S. The WATER study: Which AquaTic ExeRcises increase muscle activity and limit pain for people with low back pain? Physiotherapy. 2022;116:108-18.
422. Vasić D, Novaković M, Božič Mijovski M, Barbič Žagar B, Jug B. Short-term water- and land-based exercise training comparably improve exercise capacity and vascular function in patients after a recent coronary event: A pilot randomized controlled trial. Front Physiol. 2019;10(903).
423. Jug B, Vasić D, Novaković M, Avbelj V, Lea R, Kšela J. The effect of aquatic exercise training on heart rate variability in patients with coronary artery disease. J Cardiovasc Dev Dis. 2022;9(8):251.

424. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Training-induced increase in nitric oxide metabolites in chronic heart failure and coronary artery disease: an extra benefit of water-based exercises? Eur J Cardiovasc Prev Rehabil. 2009;16:215-21.
425. Teffaha D, Mourot L, Vernochet P, Ounissi F, Regnard J, Monpere C, et al. Relevance of water gymnastics in rehabilitation programs in patients with chronic heart failure or coronary artery disease with normal left ventricular function. J Card Fail. 2011;17:676-83.
426. Tokmakidis SP, Spassis AT, Volaklis KA. Training, detraining and retraining effects after a water-based exercise program in patients with coronary artery disease. Cardiology. 2008;111(4):257-64.
427. Lee J-Y, Joo K-C, Brubaker PH. Aqua walking as an alternative exercise modality during cardiac rehabilitation for coronary artery disease in older patients with lower extremity osteoarthritis. BMC Cardiovasc Disord. 2017;17.
428. Fiogbé E, Ferreira R, Sindorf MAG, Tavares SA, de Souza KP, de Castro Cesar M, et al. Water exercise in coronary artery disease patients, effects on heart rate variability, and body composition: A randomized controlled trial. Physiother Res Int. 2018;23(3):1.
429. Cugusi L, Manca A, Bassareo PP, Crisafulli A, Deriu F, Mercuro G. Supervised aquatic-based exercise for men with coronary artery disease: a meta-analysis of randomised controlled trials. Eur J Prev Cardiol. 2019:2047487319878109.
430. Haynes A, Naylor LH, Carter HH, Spence AL, Robey E, Cox KL, et al. Land-walking vs. water-walking interventions in older adults: Effects on aerobic fitness. J Sport Health Sci. 2020;9(3):274-82.
431. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, Dalleck LC. Graded exercise testing protocols for the determination of VO2max: Historical perspectives, progress, and future considerations. J Sports Med. 2016;2016:3968393.
432. Swift DL, Weltman JY, Patrie JT, Saliba SA, Gaesser GA, Barrett EJ, et al. Predictors of improvement in endothelial function after exercise training in a diverse sample of postmenopausal women. J Womens Health. 2014;23(3):260-6.
433. Graham LN, Smith PA, Stoker JB, Mackintosh AF, Mary DASG. Time course of sympathetic neural hyperactivity after uncomplicated acute myocardial infarction. Circulation. 2002;106(7):793-7.
434. Niemelä MJ, Airaksinen KEJ, Huikuri HV. Effect of Beta-blockade on heart rate variability in patients with coronary artery disease. J Am Coll Cardiol. 1994;23(6):1370-7.
435. Fox KM, Ferrari R. Heart rate: a forgotten link in coronary artery disease? Nat Rev Cardiol. 2011;8(7):369-79.
436. Ma R, Gao J, Mao S, Wang Z. Association between heart rate and cardiovascular death in patients with coronary heart disease: A NHANES-based cohort study. Clin Cardiol. 2022;45(5):574-82.
437. Münzel T, Hahad O, Gori T, Hollmann S, Arnold N, Prochaska JH, et al. Heart rate, mortality, and the relation with clinical and subclinical cardiovascular diseases: results from the Gutenberg Health Study. Clin Res Cardiol. 2019;108(12):1313-23.
438. Alkatan M, Machin DR, Baker JR, Akkari AS, Park W, Tanaka H. Effects of swimming and cycling exercise intervention on vascular function in patients with osteoarthritis. Am J Cardiol. 2016;117(1):141-5.
439. Klonizakis M, Mitropoulos A. Assessing the effect of regular swimming exercise on the micro- and macrovascular physiology of older adults (ACELA II study). Front Physiol. 2023;14.
440. Nualnim N, Parkhurst K, Dhindsa M, Tarumi T, Vavrek J, Tanaka H. Effects of swimming training on blood pressure and vascular function in adults >50 years of age. Am J Cardiol. 2012;109(7):1005-10.
441. Suntraluck S, Tanaka H, Suksom D. The relative efficacy of land-based and water-based exercise training on macro- and microvascular functions in older patients with type 2 diabetes. J Aging Phys Act. 2017;25(3):446.
442. Nuttamonwarakul A, Amatyakul S, Suksom D. Effects of water-based versus land-based exercise training on cutaneous microvascular reactivity and C-reactive protein in older women with type 2 diabetes mellitus. J Exerc Physiol Online. 2014;17(4):27-33.
443. Scheer AS, Naylor LH, Gan SK, Charlesworth J, Benjanuvatra N, Green DJ, et al. The effects of water-based exercise training in people with type 2 diabetes. Med Sci Sports Exerc. 2020;52(2):417-24.
444. Park S-Y, Wong A, Son W-M, Pekas EJ. Effects of heated water-based versus land-based exercise training on vascular function in individuals with peripheral artery disease. J Appl Physiol. 2020;128(3):565-75.

445. Cruz LGdB, Bocchi EA, Grassi G, Guimaraes GV. Neurohumoral and endothelial responses to heated water-based exercise in resistant hypertensive patients. Circ J. 2017;81(3):339-45.
446. Haynes A, Naylor LH, Spence AL, Robey E, Cox KL, Maslen BA, et al. Effects of land- vs water-walking interventions on vascular function in older adults. Med Sci Sports Exerc. 2021;53(1):83-9.
447. Lambert BS, Greene NP, Carradine AT, Joubert DP, Fluckey JD, Riechman SE. Aquatic treadmill training reduces blood pressure reactivity to physical stress. Med Sci Sports Exerc. 2014;46(4):809-16.
448. Natali A, Ferrannini E. Endothelial dysfunction in type 2 diabetes. Diabetologia. 2012;55(6):1559-63.
449. Thijssen DHJ, Dawson EA, Black MA, Hopman MTE, Cable NT, Green DJ. Brachial artery blood flow responses to different modalities of lower limb exercise. Med Sci Sports Exerc. 2009;41(5):1072-9.
450. Heiss C, Rodriguez-Mateos A, Kelm M. Central role of eNOS in the maintenance of endothelial homeostasis. Antioxid Redox Signal. 2015;22(14):1230-42.
451. Green D, Kurt. S, Maslen B, Cox K, Lautenshlager N, Pestell C, et al. The impact of six-month land versus water walking on cerebrovascular function in the aging brain. Med Sci Sports Exerc. 2021 53(10):2093-100.
452. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559.
453. Cider Å, Schaufelberger M, Stibrant Sunnerhagen K, Andersson B. Aquatic exercise is effective in improving exercise performance in patients with heart failure and type 2 diabetes mellitus. J Evid Based Complementary Altern Med. 2012;2012:8.
454. Adsett J, Morris N, Kuys S, Hwang R, Mullins R, Khatun M, et al. Aquatic exercise training is effective in maintaining exercise performance in trained heart failure patients: A randomised crossover pilot trial. Heart Lung Circ. 2017;26(6):572-9.
455. Korzeniowska-Kubacka I, Bilinska M, Dobraszkiewicz-Wasilewska B, Baranowski R, Piotrowicz E, Piotrowicz R. The influence of water-based training on arrhythmia in patients with stable coronary artery disease and preserved left ventricular function. Cardiol J. 2016;23(1):93-9.
456. Colado JC, Triplett NT. Monitoring the intensity of aquatic resistance exercises with devices that increase the drag force: An update. Strength Cond J. 2009;31(3):94-100.
457. Pöyhönen T, Keskinen KL, Kyröläinen H, Hautala A, Savolainen J, Mälkiä E. Neuromuscular function during therapeutic knee exercise under water and on dry land. Arch Phys Med Rehabil. 2001;82(10):1446-52.
458. Maiorana A, Driscoll G, Dembo L, Cheetham C, Goodman C, Taylor R, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. American Journal of Physiology - Heart and Circulatory Physiology. 2000;279(4):H1999-H2005.
459. Song JA, Oh JW. Effects of aquatic exercises for patients with osteoarthritis: Systematic review with meta-analysis. Healthcare (Basel). 2022;10(3):560.

Chapter 3. The effects of water-based circuit training exercise on aerobic fitness, strength and body composition in patients with stable coronary heart disease

This chapter has been published in the Journal of Physiotherapy:

Scheer A, Shah A, Ito Ramos de Oliveira B, Moreno-Suárez I, Jacques A, Green D, and Maiorana A. Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial. Journal of Physiotherapy 67: 284-290, 2021.

This information is contained in Appendix J.33.

Table 3.1 Attribution statement for Chapter 3

	Conception and design	Acquisition of data and method	Data conditioning	Analysis and statistical method	Interpretation and discussion
Anna Scheer	X	X	X	X	X
Amit Shah	X	X			
Beatriz IR de Oliviera	X			X	X
José Ignacio Moreno-Suárez		X			
Angela Jacques	X			X	
Daniel J. Green	X	X			X
Andrew Maiorana	X	X	X	X	X

All authors critically revised the manuscript.

For the research paper:

“Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial”

I confirm that Anna Scheer developed the concept of the study and contributed to the design of the project. She developed the water-based exercise training program and equipment, she drafted funding applications, completed ethics and governance applications, recruited participants, and collected the data for the study. In consultation with Angela Jacques, she performed the statistical analysis. Anna provided the initial interpretation of the data, the first draft of the manuscript and contributed to manuscript revisions.

Beatriz Ito Ramos de Oliveira

Amit Shah

José Ignacio Moreno-Suárez

Angela Jacques

Daniel J. Green

Andrew Maiorana

3.1 Abstract

Question: In people with stable coronary heart disease, what are the effects of water-based circuit training exercise on aerobic capacity, strength and body composition? How do these effects compare to those of gym-based exercise?

Design: Parallel group, randomised, controlled trial with concealed allocation and intention-to-treat analysis.

Participants: Fifty-two participants with stable coronary heart disease.

Interventions: Twelve weeks of: three 1-hour sessions per week of moderate intensity water-based circuit training exercise with alternating aerobic and resistance stations (WEX); three 1-hour sessions per week of moderate intensity gym-based circuit training exercise (GEX); or continuing usual activities (control).

Outcome measures: Aerobic capacity (VO_{2peak}), upper and lower limb one repetition maximum strength (biceps curl, latissimus dorsi pulldown, hamstring curl, leg press), anthropometry (weight, body mass index, girths) and dual energy x-ray absorptiometry (DXA).

Results: Forty-five participants completed the study (WEX n = 15, GEX n = 18, control n = 12). Both training groups significantly improved VO_{2peak} compared with control: WEX by 2.5 mL/kg/min (95% CI 0.6 to 4.4) and GEX by 2.3 mL/kg/min (95% CI 0.6 to 4.0). WEX and GEX improved hamstring strength compared to control: WEX by 6.3 kg (95% CI 1.2 to 11.3) and GEX by 7.6 kg (95% CI 2.9 to 12.2). Compared with control, GEX increased leg press strength by 15.5 kg (95% CI 5.7 to 25.3) whereas the effect of WEX was less clear (MD 7.1 kg, 95% CI –3.5 to 17.7). Only GEX improved latissimus dorsi pulldown strength. Compared with control, total body fat was reduced with WEX (–1.1 kg, 95% CI –2.3 to 0.0) and GEX (–1.2 kg, 95% CI –2.3 to –0.1). There were negligible between-group differences in weight or waist circumference.

Conclusion: WEX was well tolerated and improved aerobic capacity, leg strength and body fat to a similar degree as GEX in people with CHD. These findings suggest that WEX is an effective exercise training alternative to GEX for people with CHD.

Trial registration: ANZCTR12616000102471.

Key words: Hydrotherapy; Coronary artery disease; Circuit-based exercise; Muscle strength; Cardiorespiratory fitness.

3.2 Introduction

Exercise participation and higher levels of aerobic fitness have been associated with reduced mortality and morbidity in people with coronary heart disease (CHD) (1,2). As such, exercise training has become an important component of CHD management (3,4). Guidelines recommend accumulating 150 to 300 minutes per week of moderate-intensity physical activity, 75 to 150 minutes of vigorous-intensity physical activity, or an equivalent combination, along with muscle strengthening exercises on ≥ 2 days per week (5). Despite the established benefits of exercise in people with CHD, many do not undertake sufficient physical activity to meet guidelines (6,7).

Physical activity is particularly low in people with CHD who have comorbid conditions such as arthritis or obesity (8,9). This is concerning, given that arthritis is experienced by over half of the CHD population (9) and approximately two-thirds of people with CHD are overweight or obese (10). The high prevalence of these comorbidities suggests that low-impact exercise strategies may be beneficial for many people with CHD (11). Water-based exercise presents one such option due to the effects of buoyancy on reducing the weight bearing load on the lower limbs and spine (12).

It was recently reported that an aquatic exercise training circuit with integrated aerobic and resistance exercises improved strength and aerobic fitness in people with type 2 diabetes (13). However, there are currently very few randomised controlled studies with a duration of > 3 weeks comparing water-based exercise with gym-based exercise in people with CHD. The only study with a duration > 3 weeks comparing water-based and gym-based exercise found promising improvements in body weight, skinfolds, exercise test time and maximum strength in people with CHD following water-based exercise that were similar to those observed with gym exercise (14). However, this study was limited by the lack of gold-standard outcome measures such as peak oxygen uptake and imaging-derived body composition measures.

This study aimed to investigate the effect of 12 weeks of water-based circuit training exercise (WEX) training compared with 12 weeks of gym-based circuit training exercise (GEX) training at a similar intensity, to determine if water-based exercise is an effective alternative to the widely prescribed approach of gym-based exercise for people with CHD.

Therefore, the research questions for this randomised controlled trial were:

1. In people with stable coronary heart disease, what are the effects of water-based circuit training exercise on aerobic capacity, strength and body composition?
2. How do the effects compare with those of gym-based exercise?

3.3 Method

3.3.1 Design

This was a three-arm, parallel group, randomised controlled trial with concealed allocation and intention-to-treat analysis. Participants underwent baseline assessments prior to group allocation. The blocked random allocation list was weighted towards the two experimental groups and concealed in opaque and sealed envelopes. Participants were allocated to continue their allocated intervention (WEX or GEX three times per week, or continuing usual activities for the control group) for 12 weeks, before reassessment within 2 weeks of the final training session. The nature of the exercises prevented blinding of participants. Recruitment occurred from December 2016 to March 2019. Data collection was completed in July 2019.

3.3.2 Participants, therapists, centre

Participants were recruited through hospital databases and community advertising (Figure 3.1). The inclusion criteria were: a diagnosis of CHD (based on a previous myocardial infarction, percutaneous coronary intervention, diagnostic imaging showing ≥ 50% occlusion of ≥ 1 coronary artery, or coronary artery bypass graft surgery); stable medication for ≥ 1 month; and ≥ 6 months after any coronary event or surgery. Participants were excluded if they: had an ejection fraction < 45%: had severe musculoskeletal, respiratory or neurological impairment that would limit exercise training; had received current or recent (within 6 months) chemotherapy or radiotherapy for cancer treatment; had displayed an adverse response on baseline exercise testing (ie, ischaemic signs or symptoms at a workload of < 4 METs, new-onset left bundle branch block or ventricular tachyarrhythmia); had baseline blood test results suggesting significant other health issues; had participated in a supervised exercise program in the past 3 months; were current smokers; or were using insulin.

Assessments and exercise training sessions were conducted in a tertiary hospital outpatient setting in Perth, Australia, by a physiotherapist or an accredited exercise physiologist. Therapists were not blinded for the assessments. All water-based exercise

sessions were supervised by at least two people (at least one physiotherapist or exercise physiologist).

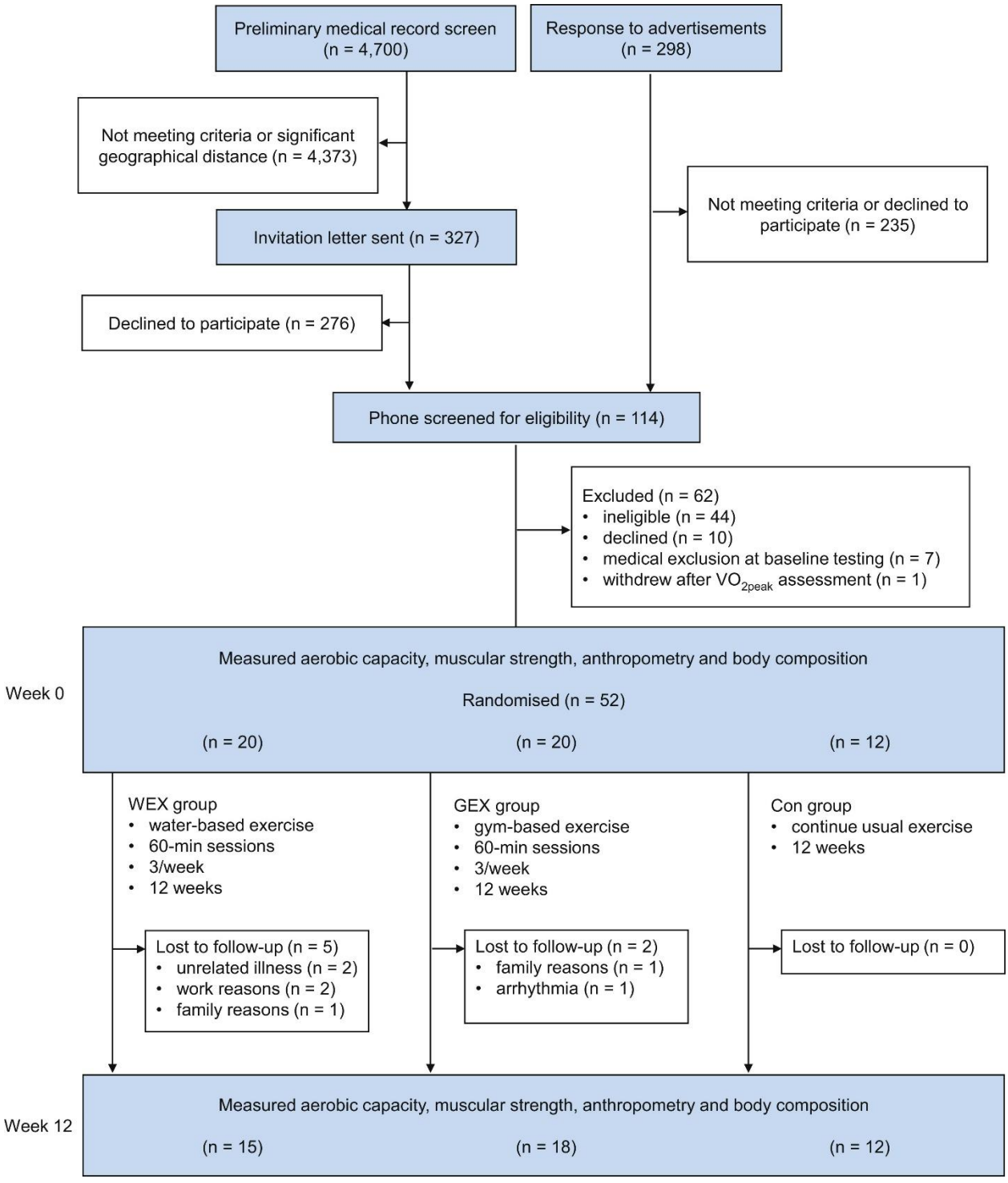


Figure 3.1 Design and flow of participants through the study.

3.3.3 Intervention

Regardless of which intervention group they were randomised to, participants were asked to maintain their usual diet throughout the study. Any medication changes during the study were documented.

3.3.4 Exercise training programs

The WEX and GEX participants trained 3 days per week for approximately 1 hour per session. All sessions commenced and concluded with 5 minutes of light aerobic activity and stretching. The conditioning phase involved a circuit of alternating aerobic and resistance exercise stations (45 seconds work, 15 seconds active recovery). Sessions progressed over the first 3 weeks from one to three circuits per session. Aerobic exercise intensity commenced at 50 to 65% of measured heart rate maximum in weeks 1 and 2, and increased to 60 to 65% in weeks 3 and 4, 60 to 70% in weeks 5 and 6, 70 to 80% in weeks 7 and 8, and 80% in weeks 9 to 12. Heart rate was monitored using wrist-worn monitors with chest straps[a]. Rating of perceived exertion (RPE) was also used to guide exercise prescription and was progressed from 11 to 14 over the course of training (15). Resistance exercises were matched for muscle group between WEX and GEX, and the range of motion of the arm exercises for both groups was limited to the range allowed by the water level of the WEX group. Resistance exercise RPE targets were 12 to 15.

The WEX group trained in a graded-depth hydrotherapy pool (34.5 °C) and were submersed to the xiphoid process. Aerobic exercises included walking/jogging and high knee lifts. Strength exercises included unilateral knee flexion/extension, unilateral hip flexion/extension, unilateral hip abduction/adduction (with the side of this exercise alternated at each circuit), bilateral elbow flexion/extension, and bilateral shoulder abduction/adduction (limited by water depth). More details are presented in Appendix 1 on the eAddenda (see Figure 3.2). The resistance was provided by custom-designed paddles, using acrylic sheets either side of the limb, fastened by hook and loop fasteners or buckles, ranging from 15 x 20 cm to 30 x 35 cm (Appendix 1 on the eAddenda, see Figure 3.2). Resistance was progressed by increasing the speed of movement guided by waterproof metronomes worn by participants on headbands[b] whilst maintaining the same range of movement. Exercises were progressed to include larger paddle sizes once participants were able to maintain the set pace per repetition with good technique and Borg RPE fell below 13.

The GEX group exercised in a cardiac rehabilitation outpatient gymnasium. Aerobic exercises involved stationary cycling and treadmill walking. Strength exercises involved bilateral knee extension, bilateral latissimus pulldown, bilateral knee flexion, unilateral hip flexion/extension, bilateral triceps[c], unilateral hip abduction/adduction with ankle weights[d], bilateral biceps and bilateral shoulder abduction with dumbbells (limited to the height of the xiphoid process). Resistance exercises were initially prescribed at approximately 50% one repetition maximum (1RM). Participants commenced with 10 repetitions and progressed to the next weight once they could achieve 12 to 15 repetitions in 45 seconds, with good technique and at an RPE < 13. Due to the concentric-only nature of the WEX training, biceps and triceps and shoulder abduction and latissimus pulldown were alternated each circuit in the GEX program, so that after two consecutive sessions the time training each muscle group was matched between the WEX and GEX groups.

3.3.5 Control group

Participants in the control group were instructed to maintain their usual activities throughout the study and were offered an optional gym-based exercise program or home exercise advice at the completion of the study.

3.3.6 Outcome measures

3.3.6.1 Primary outcome

The primary outcome was aerobic exercise capacity (VO_{2peak}).

3.3.6.2 Secondary outcomes

Aerobic exercise capacity (VO_{2peak}) was assessed by indirect calorimetry[e] using a modified chronotropic protocol on a treadmill[f] with increases in speed and incline every 3 minutes. Participants were monitored with a 12-lead ECG[g]. The metabolic cart was calibrated according to standard procedures prior to each assessment. The test continued until volitional exhaustion, unless terminated by the supervising doctor.

Muscular strength was assessed with 1RM assessments for bicep curl using a dumbbell[h] and for latissimus pulldown, leg press and hamstring curl using seated weight stack machines[i] and the machine settings at baseline were used for follow-up assessments for reproducibility. Participants were instructed to avoid a Valsalva manoeuvre throughout strength testing. Participants initially conducted six repetitions of a light weight for a muscle-

specific warm-up, followed by 1-minute rest, then two repetitions of a moderate weight followed by a 1-minute rest. Subsequently, progressively heavier weights were lifted once with 2 minutes rest between repetitions, with the last successful repetition that could be lifted through a full range of motion recorded as the 1RM.

Anthropometric measures included weight, body mass index (BMI), waist circumference and hip circumference. Body weight was measured by digital scales[j]. Waist and hip girth measurements were taken in triplicate, with the median used for analysis. Dual energy x-ray absorptiometry (DXA) was used to measure body mass, body fat and bone mineral density. The DXA scan was performed on a body scanner[k] after ≥ 6-hour fast (16). Standard procedure of omitting the right arm and duplicating the left arm was used if a participant was too large to fit on the DXA bed.

3.3.7 Data analysis

Sample size was based on data from Tokmakidis et al (17), who found that water-based exercise training over 4 months increased VO_{2peak} in people with CHD from 26.2 (SD 4.0) to 28.4 (SD 4.9) ml/kg/min (17). The calculated Cohen's d was 0.48,(18) with an effect size of 0.24 (19). Assuming 90% power and a 5% level of significance, and a conservative estimated correlation among repeated measures of 0.75 (based on our previous study of water-based exercise for people with type 2 diabetes) (13), the estimated total sample size was 33 (ie, 11 per group for a repeated measures ANOVA (mixed model) with three groups over two timepoints)[l]. To allow for training program withdrawals, recruitment targets were set at 20 per group for the training groups.

Results were analysed with commercial software[m]. Generalised linear mixed models with appropriate links were used for within-group pre-post assessments and group-time interactions. Mixed effects Tobit models were used for leg press and hamstring data due to ceiling effects in those outcomes.

3.4 Results

3.4.1 Flow of participants and therapists through the study

Participant flow through the study is presented in Figure 3.1. Participant characteristics are described in Table 3.2. There was one adverse event during the study: a GEX participant with a history of supraventricular tachycardia experienced an episode of it during training in week 8 of his program. He received immediate medical attention and

recovered fully that day, although he withdrew from the study to undergo an elective ablation procedure.

Aerobic capacity assessments were incomplete for three WEX participants (one due to illness, one injured outside the study and one unable to tolerate a mask or mouthpiece). Muscular strength assessments were incomplete for one WEX and one control participant due to illness. Due to musculoskeletal limitations, paired data were unavailable for leg press in three WEX, two GEX and two control participants; hamstring curl in two WEX and one control participant; biceps curl in one WEX, two GEX and one control participant; and latissimus pulldown in four WEX, three GEX and three control participants. DXA scans were not available for one WEX, one GEX and one control participant due to machine servicing/unavailability, and one control participant due to illness. DXA data were incomplete in one WEX participant due to artefact.

Table 3.2 Baseline characteristics of participants.

Characteristic	Completed (n = 45)			Lost to follow-up (n = 7)	
	WEX (n = 15)	GEX (n = 18)	Con (n = 12)	WEX (n = 5)	GEX (n = 2)
Age (*yr*), mean (SD)	66 (8)	67 (8)	71 (5)	66 (5)	66 (7)
Gender, n males (%)	12 (80)	16 (89)	9 (75)	3 (60)	2 (100)
Time since diagnosis *(yr)*					
median	3.3	2.3	5.5	4.0	11.2
range	0.8 to 15	0.5 to 29	0.5 to 18	1.3 to 9	2.4 to 20
Medical history, n (%)					
cancer (other than skin)	1 (7)	5 (28)	2 (17)	1 (20)	0 (0)
type 2 diabetes	1 (7)	1 (6)	3 (25)	0 (0)	0 (0)
pre-diabetes	1 (7)	3 (17)	0 (0)	0 (0)	1 (50)
stroke	1 (7)	0 (0)	2 (17)	0 (0)	0 (0)
transient ischaemic attack	0 (0)	1 (6)	1 (8)	0 (0)	0 (0)
peripheral vascular disease	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)
arthritis	5 (33)	4 (22)	3 (25)	2 (40)	0 (0)
non-specified joint pain	6 (40)	4 (22)	6 (50)	3 (60)	2 (100)
respiratory condition	2 (13)	4 (22)	3 (25)	2 (40)	0 (0)
Cardiac history, n (%)					
silent	3 (20)	2 (11)	2 (17)	0 (0)	0 (0)
angina only	4 (27)	7 (39)	5 (42)	1 (20)	0 (0)
myocardial infarction	8 (53)	9 (50)	5 (42)	4 (80)	2 (100)
Treatment, n (%)					
CABG	2 (13)	7 (39)	6 (50)	0 (0)	1 (50)
PCI	11 (73)	14 (78)	7 (58)	5 (100)	1 (50)

CABG and PCI	0 (0)	3 (17)	2 (17)	0 (0)	0 (0)
medication only	2 (13)	0 (0)	2 (17)	0 (0)	0 (0)
Medication, n (%)					
beta blockers	5 (33)	7(39)	9 (75)	1 (20)	1 (50)
lipid lowering	14 (93)	17 (94)	11 (92)	4 (80)	2 (100)
glucose lowering	0 (0)	1 (6)	3 (25)	0 (0)	0 (0)
antiplatelet/anticoagulant	15 (100)	17 (94)	12 (100)	5 (100)	2 (100)
ACE inhibitors	5 (33)	10 (56)	4 (33)	1 (20)	2 (100)
angiotensin II receptor blockers	4 (27)	4 (22)	5 (42)	2 (40)	0 (0)
calcium channel blockers	1 (7)	3 (17)	3 (25)	3 (60)	0 (0)
diuretic	0 (0)	1 (6)	1 (8)	1 (20)	0 (0)
proton pump inhibitors	5 (33)	4 (22)	5 (42)	2 (40)	1 (50)

ACE = angiotensin converting enzyme, CABG = coronary artery bypass graft surgery, Con = control, GEX = gym-based exercise, PCI = percutaneous coronary intervention, Silent = picked up on investigation without prior cardiac symptoms, WEX = water-based exercise

3.4.2 Research question 1

Water-based exercise improved the primary outcome – aerobic capacity – by a mean of 2.5 ml/kg/min (95% CI 0.6 to 4.4) (Table 3.3). Water-based exercise also improved a measure of leg strength (mean difference in 1RM hamstring curl of 6.3 kg, 95% CI 1.2 to 11.3) (Table 3.3). Water-based exercise also reduced total body fat by a mean of 1.1 kg (95% CI 0.0 to 2.3) (Table 3.4). Water-based exercise induced no clear changes in upper body strength or anthropometric measures (Table 3.3, Table 3.4).

3.4.3 Research question 2

Both modes of exercise training improved exercise capacity (VO_{2peak}) to a similar extent and GEX increased exercise time (Table 3.3). Both WEX and GEX increased leg strength, but only GEX significantly improved latissimus pulldown strength (Table 3.3). Body fat decreased with both types of exercise training over time, with a negligible difference between the effects of the two types of training (Table 3.4).

The results from all participants who completed baseline testing are available in Table 3.5 Appendix 2 (aerobic capacity and strength testing) and Table 3.6 Appendix 3 (body composition) on the eAddenda. Individual participant data are presented in Table 4 on the eAddenda.

Table 3.3 Aerobic capacity and muscular strength.

Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups for paired aerobic capacity and muscular strength data.

Outcome	Groups						Difference within groups			Difference between groups[a]		
	Week 0			Week 12			Week 12 minus Week 0			Week 12 minus Week 0		
	WEX	GEX	Con	WEX	GEX	Con	WEX	GEX	Con	WEX minus Con	GEX minus Con	WEX minus GEX
VO_{2peak} *(mL/kg/min)*	29.1 (8.9)	26.3 (5.5)	24.6 (6.7)	30.9 (9.1)	27.9 (5.8)	23.9 (5.9)	1.8 (2.6)	1.6 (1.9)	–0.7 (2.6)	2.5 (0.6 to 4.4)	2.3 (0.6 to 4.0)	0.2 (–1.5 to 1.9)
VO_{2peak} *(mL/min)*	2398 (616)	2188 (383)	1970 (594)	2502 (571)	2302 (384)	1915 (576)	104 (242)	114 (128)	–55 (239)	166 (16 to 317)	167 (30 to 305)	–1 (–138 to 136)
Percent of predicted VO_2 maximum	104.2 (23.5)	97.4 (21.5)	97.8 (20.4)	110.6 (24.9)	103.3 (21.7)	95.0 (15.4)	6.4 (9.9)	5.9 (7.2)	–2.8 (7.4)	9.5 (2.5 to 16.5)	8.7 (2.3 to 15.1)	0.8 (–5.5 to 7.2)
Exercise duration *(s)*	942 (184)	843 (116)	831 (233)	998 (220)	946 (120)	867 (174)	56 (83)	103 (39)	36 (84)	22 (–35 to 79)	68 (16 to 121)	–47 (–98 to 5)
VCO_{2peak} *(mL/min)*	2679 (703)	2392 (526)	2117 (683)	2836 (654)	2620 (581)	2090 (624)	157 (277)	228 (185)	–27 (267)	195 (9 to 381)	253 (83 to 424)	–58 (–228 to 112)
V_E/VCO_2 slope	28.9 (3.9)	27.6 (4.1)	29.6 (3.5)	29.0 (3.4)	27.8 (4.0)	28.7 (3.4)	0.1 (1.6)	0.2 (1.4)	–0.9 (1.5)	1.1 (–0.8 to 3.0)	1.1 (–0.7 to 2.8)	–0.0 (–1.7 to 1.7)
RER	1.12 (0.07)	1.09 (0.08)	1.07 (0.08)	1.14 (0.08)	1.13 (0.10)	1.10 (0.06)	0.02 (0.03)	0.04 (0.03)	0.03 (0.03)	–0.01 (–0.05 to 0.04)	0.01 (–0.03 to 0.05)	–0.02 (–0.06 to 0.02)
RPE	17 (2)	18 (2)	17 (1)	17 (2)	18 (2)	17 (2)	0 (1)	0 (1)	0 (1)	–1 (–2 to 0)	0 (–1 to 1)	–1 (–2 to 0)
Bicep curl 1RM *(kg)*	11.4 (4.4)	10.1 (3.5)	9.0 (2.7)	11.2 (4.2)	11.1 (3.6)	9.2 (3.0)	–0.2 (1.7)	1 (1.3)	0.2 (1.3)	–0.4 (–1.4 to 0.7)	0.7 (–0.3 to 1.7)	–1.0 (–2.0 to –0.1)
Latissimus pulldown 1RM *(kg)*	45.0 (12.7)	41.3 (10.9)	38.8 (9.5)	47.0 (10.9)	47.0 (12.1)	40.0 (8.5)	2 (5.3)	5.7 (4.2)	1.2 (4.5)	0.6 (–3.7 to 4.8)	4.2 (0.3 to 8.1)	–3.6 (–7.3 to 0.0)
Hamstring curl 1RM *(kg)*	49.9 (12.5)	50.6 (12.4)	44.6 (9.8)	55.1 (16.0)	57.3 (12.1)	43.4 (11.1)	5.2 (5.9)	6.7 (4.1)	–1.2 (11.1)	6.3[b] (1.2 to 11.3)	7.6 [b] (2.9 to 12.2)	–1.3 [b] (–5.8 to 3.2)
Leg press 1RM *(kg)*	124.0 (37.0)	121.5 (33.6)	122.5 (44.8)	132.1 (39.9)	138.2 (31.4)	123.5 (49.2)	8.1 (16.4)	16.7 (11.5)	1 (22.2)	7.1 [b] (–3.5 to 17.7)	15.5 [b] (5.7 to 25.3)	–8.4 [b] (–17.6 to 0.8)

Con = control group, GEX = gym–based exercise training group, RER = respiratory exchange ratio, RPE = rating of perceived exertion, VCO_{2peak}= peak carbon dioxide output, VO_{2peak} = peak oxygen uptake, WEX = water-based exercise training group, 1RM = one repetition maximum strength.
[a] Difference between estimated margins of means using general linear mixed model analysis.[b] Metobit analysis used.

Table 3.4 Anthropometry and body composition.

Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups for paired anthropometry and body composition data.

Outcome	Groups						Difference within groups			Difference between groups[a]		
	Week 0			Week 12			Week 12 minus Week 0			Week 12 minus Week 0		
	WEX	GEX	Con	WEX	GEX	Con	WEX	GEX	Con	WEX minus Con	GEX minus Con	WEX minus GEX
Anthropometry												
Weight *(kg)*	85.2 (13.9)	84.7 (12.9)	80.3 (10.4)	84.4 (14.1)	83.8 (12.1)	80.1 (10.7)	–0.8 (5.1)	–0.9 (4.2)	–0.2 (4.3)	–0.6 (–2.0 to 0.8)	–0.7 (–2.1 to 0.6)	0.1 (–1.1 to 1.4)
BMI *(kg/cm^2)*	29.1 (4.2)	28.4 (3.9)	28.0 (3.7)	28.8 (4.3)	28.1 (3.7)	27.9 (3.5)	–0.3 (1.6)	–0.3 (1.3)	–0.1 (1.5)	–0.2 (–0.6 to 0.3)	–0.2 (–0.7 to 0.3)	0.0 (–0.4 to 0.5)
Waist girth *(cm)*	100.6 (12.5)	102.8 (10.7)	101.5 (8.6)	100.2 (11.8)	101.2 (9.9)	101.6 (9.9)	–0.4 (4.4)	–1.6 (3.4)	0.1 (3.9)	–0.4 (–2.8 to 1.9)	–1.7 (–3.9 to 0.6)	1.2 (–0.8 to 3.3)
Hip girth *(cm)*	107.9 (7.4)	105.6 (6.2)	104.5 (6.9)	107.1 (8.7)	104.4 (5.8)	103.9 (7.5)	–0.8 (2.9)	–1.2 (2)	–0.6 (3.1)	–0.1 (–2.1 to 1.9)	–0.6 (–2.5 to 1.4)	0.4 (–1.3 to 2.2)
Waist:hip ratio	0.93 (0.09)	0.97 (0.07)	0.97 (0.06)	0.94 (0.07)	0.97 (0.06)	0.98 (0.08)	0.01 (0.03)	0.00 (0.02)	0.01 (0.03)	–0.00 (–0.03 to 0.02)	–0.01 (–0.04 to 0.01)	0.01 (–0.02 to 0.03)
DXA data												
Total mass *(kg)*	85.3 (14.7)	83.8 (13)	79.7 (11.4)	83.9 (14.9)	83.2 (12.4)	80.1 (11.9)	–1.4 (5.8)	–0.6 (4.4)	0.4 (5.2)	–1.8 (–3.3 to –0.4)	–1.2 (–2.5 to 0.2)	–0.7 (–1.9 to 0.6)
Total fat *(kg)*	29.5 (12.0)	28.6 (7.0)	27.1 (8.0)	28.5 (12.1)	27.6 (6.7)	27.3 (8.2)	–0.9 (4.7)	–1.0 (2.4)	0.2 (3.6)	–1.1 (–2.3 to 0.0)	–1.2 (–2.3 to –0.1)	0.1 (–0.9 to 1.1)
Tissue fat *(%)*	35.0 (11.4)	35.2 (6.1)	35.0 (7.7)	34.4 (12.1)	34.3 (6.5)	35.0 (7.5)	–0.6 (4.6)	–0.9 (2.2)	0.0 (3.4)	–0.6 (–1.6 to 0.5)	–0.8 (–1.8 to 0.2)	0.2 (–0.7 to 1.2)
Total lean *(kg)*	52.9 (9.7)	52.3 (8.6)	49.7 (8.4)	52.4 (9.9)	52.6 (9.0)	50.0 (8.2)	–0.4 (3.8)	0.3 (3.0)	0.3 (3.7)	–0.7 (–1.5 to 0.0)	0.0 (–0.7 to 0.7)	–0.7 (–1.4 to –0.1)
BMD *(g/cm^2)*	1.28 (0.15)	1.28 (0.13)	1.27 (0.19)	1.27 (0.15)	1.28 (0.12)	1.26 (0.18)	–0.01 (0.06)	0.00 (0.05)	–0.01 (0.09)	0.01 (–0.01 to 0.02)	0.01 (–0.01 to 0.02)	0.00 (–0.01 to 0.02)

GLMM= generalized linear mixed models, WEX = water-based exercise training group, GEX = gym-based exercise training group, Con = control group, BMI: body mass index; DXA: dual energy x-ray absorptiometry; BMD: bone mineral density. [a] Difference between estimated margins of means using general linear mixed model analysis

3.5 Discussion

The estimates of treatment effects generated by this study show that water-based circuit training resulted in similar benefits in aerobic capacity, leg strength and total body fat as traditionally prescribed gym-based circuit training. These findings highlight water-based exercise as an effective alternative to gym-based training for people with CHD.

It is believed that this study is the first parallel-group controlled trial to investigate the effect of water-based versus gym-based circuit training on VO_{2peak} in people with stable CHD. It found that WEX resulted in a similar magnitude improvement in VO_{2peak} to GEX, increasing by 1.8 ml/kg/min and 1.6 ml/kg/min, respectively. This is similar to DeSchutter et al's finding of a 1.9 ml/kg/min mean improvement in a large cohort trial in centre-based exercise rehabilitation (2). Whilst not a randomised controlled trial, Tokmakidis et al examined two 4-month blocks of water-based exercise training, separated by 4 months of detraining in people with CHD (17). They reported comparable increases in VO_{2peak} of 2.2 ml/kg/min and 1.8 ml/kg/min (17). There is increasing recognition that aerobic capacity is an important prognostic indicator across a range of chronic conditions (2,20). In people with CHD, a 1 ml/kg/min higher VO_{2peak} at baseline or improvement over time has been associated with a 10 to 16% improvement in cardiac and all-cause mortality (2,20,21), highlighting the importance of even modest improvements in VO_{2peak} in this population. The mean change in VO_{2peak} for both WEX and GEX exceeded 1 ml/kg/min more than the mean change in the control group, and there was no important difference in the change in VO_{2peak} for the two training types, suggesting that these forms of exercise training are equally effective.

Despite similar changes in VO_{2peak} with both types of exercise training, only GEX significantly increased exercise test time compared with the control group. A similar effect was observed in a study of 24 weeks of water-based and land-based walking in older adults (22), which found a significant increase in exercise test time with land-based walking only, despite similar VO_{2peak} changes. This may have been due to the specificity of treadmill training and land-based walking to the outcome of treadmill test duration (23), in contrast to a more generalisable effect on aerobic capacity, as measured by change in VO_{2peak}.

Both training groups experienced a similar mean reduction in fat mass. These reductions in fat mass occurred in the absence of dietary modifications. Previous studies have examined other markers of body fat, such as sum of skinfolds, and found favourable

effects of aquatic exercise on reducing body fat (14,17), which appear similar to gym exercise (14), whilst the effect on body fat measured with bioelectric impedance did not reach significance in another study (24). However, it is believed that this is the first study comparing DXA data in response to water-based exercise training compared with gym-based training in people with CHD. There were no significant pre-post differences for lean tissue data in any group; however, there was a difference in the change in lean mass observed between GEX and WEX. The individual group differences were < 450 g, which fall within the margin of accuracy of 0.61 to 0.86 kg for lean tissue changes for the scanner[k] proposed by several studies (25, 26, 27), suggesting that clarification with a larger sample is required to determine the effects on lean tissue mass. Additionally, research in older adults found that 24 weeks of water-walking significantly increased lower limb lean tissue mass compared to a control group (28), suggesting a longer duration program may be required to induce substantial lean tissue changes.

The mean improvements in leg strength with GEX equated to a 13% improvement in hamstring curl and a 14% improvement in leg press. The mean improvements with WEX equated to 10% for hamstring curl and 7% for leg press, with some uncertainty in the latter estimate (Table 3.3). For upper limb strength (latissimus pulldown), there were greater changes with GEX than WEX. This may reflect the limited range of motion for upper limb exercises during WEX due to the water depth during training (29). Buoyancy-resisted exercises may have a greater impact on upper limb strengthening in the pool and would be an interesting concept for future research. Alternatively, it may be necessary to supplement aquatic exercises with some gym-based or free weight exercises to address upper-body strength.

Other studies of WEX in CHD have reported overall strength gains of between 12 and 13% (14,17) and found similar changes between WEX and GEX (14). However, individual breakdown of muscle groups was not reported in these studies, so it is unknown if the lack of upper limb response is universal in response to WEX. Encouragingly, improvements in leg strength alone have been associated with reduced all-cause and cardiovascular mortality in people with CHD (30), suggesting that the strength changes seen in the current study are of clinical value, despite the lack of upper limb improvement.

With improved treatment for acute coronary events, increasing numbers of people are living with chronic CHD. To reduce recurrent coronary events in this group, it is important that the exercise prescription paradigm shifts from merely a focus on time-limited rehabilitation to long-term secondary prevention. The findings from this study suggest that

water-based exercise should be encouraged as one of the suite of exercise options to help people with chronic CHD be sufficiently active to achieve health and fitness benefits. Importantly, WEX was well tolerated in the cohort of participants with stable CHD, with no adverse events occurring in this group. The three sessions of WEX per week prescribed in the study is consistent with exercise training guidelines (5). In the context of community exercise participation, people may wish to undertake multiple WEX sessions or combine WEX with other modes of exercise, depending on their preference and capabilities. For example, WEX could be used as an initial entry into exercise programs for deconditioned patients or those with musculoskeletal comorbidities. Alternatively, WEX could be used as an adjunct with GEX and/or walking programs to increase exercise variety. Clinicians wishing to prescribe similar aquatic exercise programs to the WEX program investigated in this study could easily and cheaply replicate the equipment used in this study (acrylic plastic sheets, with hook and loop or buckle fastenings, as pictured in Figure 3.2 Appendix 1) or use commercially available aquatic resistance equipment. Importantly, once individual tolerance to the program is established and correct techniques have been taught, many patients would be able to continue the program independently.

This study excluded people with CHD if they also had left ventricular dysfunction, type 1 diabetes, treatment with insulin, or serious respiratory, neurological or musculoskeletal pathology, so the generalisation of the safety and efficacy for these sub-populations remains unknown. Additionally, participants were recruited ≥ 6 months after any myocardial infarction, coronary artery bypass graft surgery or percutaneous coronary intervention, so the results may not be applicable to the initial stages of cardiac rehabilitation. It is recommended that future research should examine the effects of water-based exercise in sub-acute outpatient cardiac rehabilitation. It should be noted that the resistance machines used for strength assessment of latissimus pulldowns, biceps curl and hamstring curl were the same as those employed during training. This specificity may have influenced the findings for the GEX group.

This is the first outpatient-based, parallel-group, randomised controlled trial of combined aerobic and resistance exercise comparing water-based and gym-based exercise to examine the effect on VO_{2peak} and DXA-derived body composition. The study found that water-based circuit training was well tolerated and effective for improving aerobic capacity, leg strength and fat mass, similar to gym-based exercise in people with stable CHD. This supports the expansion of exercise prescription options for people with stable CHD to

include water-based exercise, which may be useful for adding a low joint-impact exercise option to facilitate exercise engagement.

What was already known on this topic: With improved treatment for acute coronary events, increasing numbers of people are living with coronary heart disease. To reduce recurrent coronary events in this group, it is important that the exercise prescription includes a focus on long-term secondary prevention.

What this study adds: Water-based circuit training that included both aerobic and resistance stations was well tolerated and effective for improving aerobic capacity, leg strength and fat mass in people with stable coronary heart disease. The benefits were similar in magnitude to the benefits of gym-based exercise in this population.

Acknowledgements: We would like to thank Mr Eric Watson for his assistance with the pool-based training sessions and Ms Leanne Campbell for her assistance with the VO2peak assessments and training sessions.

Footnotes: [a]A300, FT4 and FT7 watches, Polar Electronics, Guangzhou, China. [b]Tempo Trainer Pro, FINIS, Tracy, USA. [c]Bravo Pulley Machine, Cybex International, Medway, USA. [d]Ankle cuff weight, Fortress Fitness, Sydney, Australia. [e]Vmax Encore Metabolic Cart, Vyntus, Vyaire Medical, Illinois, USA. [f]TMX428220, Trackmaster, Newton, USA. [g]PC ECG 1200, Norav Medical, Wiesbaden, Germany. [h]Australian Barbell Company, Australia. [i]Cybex, Cybex International, Medway, USA. [j]Seca 676 wireless scales, Seca gmbh & co, Hamburg, Germany. [k]GE Lunar iDXA, GE Healthcare, Wisconsin, USA. [l]G∗Power 3, Universität Düsseldorf, Düsseldorf, Germany. [m]STATA V16 for Windows, Microsoft, Redmond, USA.

Ethics approval: The Royal Perth Hospital Human Research Ethics Committee approved this study (ref: RGS0000002071), with reciprocal approval from Curtin University (ref: HR227/2015) and The University of Western Australia's (Ref: RA/4/1/8382) Human Research Ethics Committees. All participants gave written informed consent before data collection began.

3.6 eAddenda

These items and eAddenda Appendix 4 (excel spreadsheet of individual participant data) can be found under the Supplementary Data section with the online article with the following link: https://doi.org/10.1016/j.jphys.2021.08.012

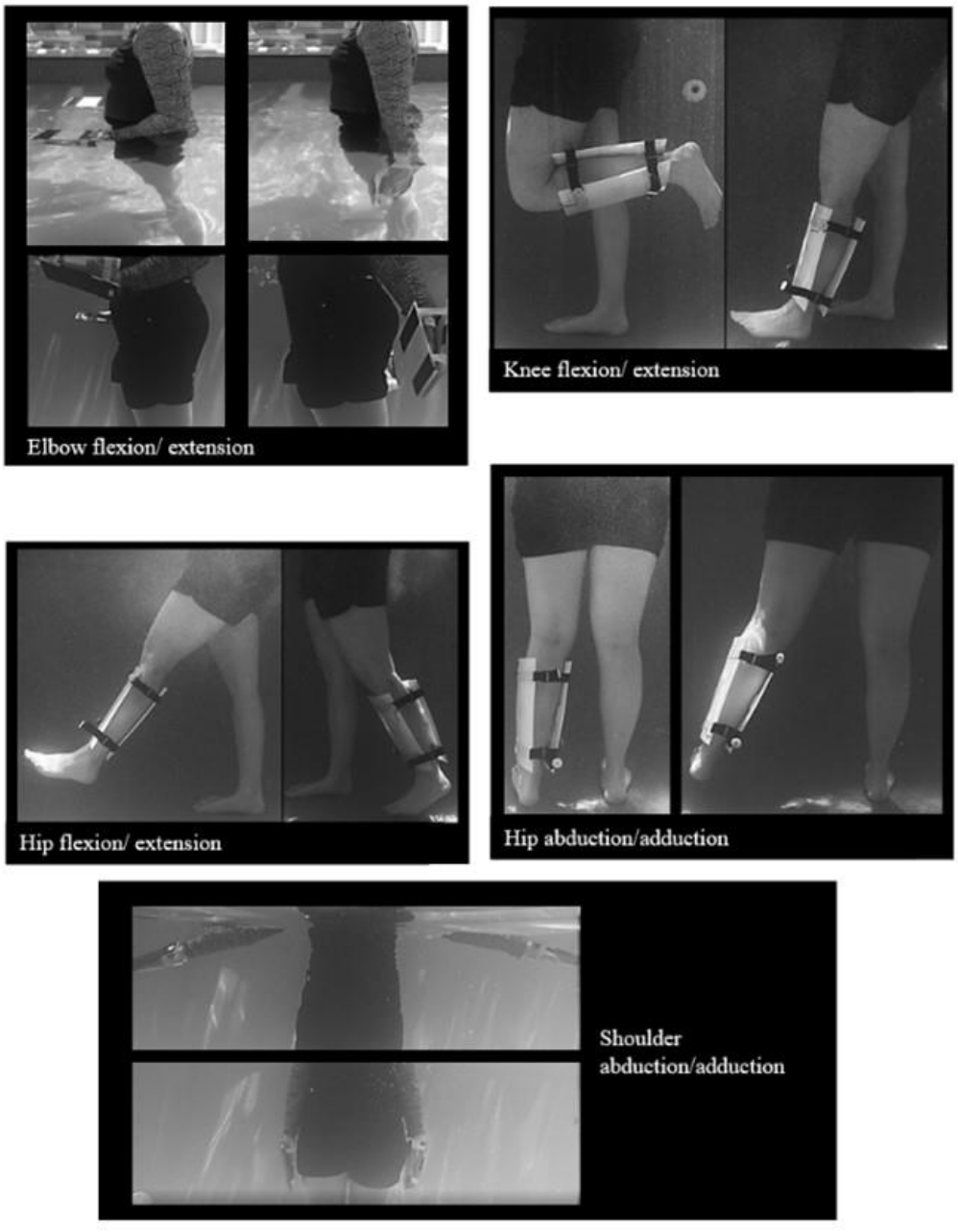


Figure 3.2 eAddenda Appendix 1. Aquatic resistance exercises and resistance exercise equipment

Table 3.5 eAddenda Appendix 2

Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups for aerobic capacity and muscular strength data (all baseline data and available follow-up data).

Outcome	Groups						Difference within groups			Difference between groups[a]		
	Week 0			Week 12			Week 12 minus Week 0			Week 12 minus Week 0		
	WEX (n = 20)	GEX (n = 20)	Con (n = 12)	WEX (n = 15)	GEX (n = 18)	Con (n = 12)	WEX	GEX	Con	WEX minus Con	GEX minus Con	WEX minus GEX
VO_{2peak} *(ml/kg/min)*	27.6 (8.0)	26.1 (5.3)	24.6 (6.7)	30.9 (9.1)	27.9 (5.8)	23.9 (5.9)	3.3 (3.3)	1.8 (1.8)	–0.7 (2.6)	2.5 (0.6 to 4.4)	2.3 (0.6 to 4.0)	0.2 (–1.5 to 1.9)
VO_{2peak} *(ml/min)*	2,281 (644)	2,217 (373)	1,970 (594)	2,502 (571)	2,302 (384)	1,915 (576)	221 (218)	85 (125)	–55 (239)	166 (16 to 317)	167 (30 to 305)	–1 (–138 to 136)
Percent of predicted VO_2 maximum	100.6 (20.9)	96.4 (20.9)	97.8 (20.4)	110.6 (24.9)	103.3 (21.7)	95.0 (15.4)	10 (8.9)	6.9 (7)	–2.8 (7.4)	9.5 (2.5 to 16.5)	8.7 (2.3 to 15.1)	0.8 (–5.5 to 7.2)
Exercise duration *(s)*	930 (190)	832 (116)	831 (233)	998 (220)	946 (120)	867 (174)	68 (76)	114 (38)	36 (84)	22 (–35 to 79)	68 (16 to 121)	–47 (–98 to 5)
VCO_{2peak} *(ml/min)*	2,522 (743)	2,427 (510)	2,117 (683)	2,836 (654)	2,620 (581)	2,090 (624)	314 (247)	193 (181)	–27 (267)	195 (9 to 381)	253 (83 to 424)	–58 (–228 to 112)
V_E/VCO_2 slope	28.3 (3.7)	27.5 (3.9)	29.5 (3.3)	29.0 (3.4)	27.8 (4.0)	28.7 (3.4)	0.7 (1.3)	0.3 (1.3)	–0.8 (1.4)	1.1 (–0.8 to 3.0)	1.1 (–0.7 to 2.8)	–0.0 (–1.7 to 1.7)
RER	1.10 (0.07)	1.09 (0.08)	1.07 (0.08)	1.14 (0.08)	1.13 (0.10)	1.10 (0.06)	0.04 (0.03)	0.04 (0.03)	0.03 (0.03)	–0.01 (–0.05 to 0.04)	0.01 (–0.03 to 0.05)	–0.02 (–0.06 to 0.02)
RPE	18 (2)	18 (1)	17 (1)	17 (2)	18 (2)	17 (2)	–1 (1)	0 (1)	0 (1)	–1 (–2 to 0)	0 (–1 to 1)	–1 (–2 to 0)
Bicep curl 1RM *(kg)*	10.4 (4.4)	10.5 (3.4)	8.7 (2.7)	11.2 (4.2)	11.1 (3.6)	9.2 (3.0)	0.8 (1.5)	0.6 (1.2)	0.5 (1.3)	–0.4 (–1.4 to 0.7)	0.7 (–0.3 to 1.7)	–1.0 (–2.0 to –0.1)
Lat. pulldown 1RM *(kg)*	45.0 (12.3)	41.8 (10.5)	36.7 (10.9)	47.0 (10.9)	47.0 (12.1)	40.0 (8.5)	2.0 (4.8)	5.2 (4.1)	3.3 (4.7)	0.6 (–3.7 to 4.8)	4.2 (0.3 to 8.1)	–3.6 (–7.3 to 0.0)
Hamstring curl 1RM *(kg)*	50.4 (15.0)	51.5 (12.7)	43.1 (10.6)	55.1 (16.0)	57.3 (12.1)	43.4 (11.1)	4.7 (5.6)	5.8 (4.0)	0.3 (4.5)	6.3[b] (1.2 to 11.3)	7.6[b] (2.9 to 12.2)	–1.3[b] (–5.8 to 3.2)
Leg press 1RM *(kg)*	125.2 (41.8)	126.7 (35.3)	121.5 (43.6)	132.1 (39.9)	140.6 (32.0)	123.5 (49.2)	6.9 (15)	13.9 (11.1)	2.0 (20.7)	7.1[b] (–3.5 to 17.7)	15.5[b] (5.7 to 25.3)	–8.4[b] (–17.6 to 0.8)

Con = control group, GEX = gym-based exercise training group, RER = respiratory exchange ratio, RPE = rating of perceived exertion, VCO_{2peak}= peak carbon dioxide output, VO_{2peak} = peak oxygen uptake, WEX = water-based exercise training group, 1RM = one repetition maximum strength, Lat. = latissimus dorsi

[a] Difference between estimated margins of means using general linear mixed model analysis.

[b] Metobit analysis used.

Table 3.6 eAddenda Appendix 3 anthropometry and body composition

Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups for anthropometry and body composition data (all baseline data and available follow-up data).

Outcome	Groups						Difference within groups			Difference between groups[a]		
	Week 0			Week 12			Week 12 minus Week 0			Week 12 minus Week 0		
	WEX (n = 20)	GEX (n = 20)	Con (n = 12)	WEX (n = 15)	GEX (n = 18)	Con (n = 12)	WEX	GEX	Con	WEX minus Con	GEX minus Con	WEX minus GEX
Anthropometry												
Weight *(kg)*	83.1 (13.5)	86.4 (13.4)	80.3 (10.4)	84.4 (14.1)	83.8 (12.1)	80.1 (10.7)	1.3 (4.8)	–2.6 (4.1)	–0.2 (4.3)	–0.6 (–2.0 to 0.8)	–0.7 (–2.1 to 0.6)	0.1 (–1.1 to 1.4)
BMI *(kg/cm^2)*	28.5 (4.1)	28.9 (4.1)	28.0 (3.7)	28.8 (4.3)	28.1 (3.7)	27.9 (3.5)	0.3 (1.5)	–0.8 (1.3)	–0.1 (1.5)	–0.2 (–0.6 to 0.3)	–0.2 (–0.7 to 0.3)	0.0 (–0.4 to 0.5)
Waist girth *(cm)*	100.2 (12)	103.8 (10.6)	101.5 (8.6)	100.2 (11.8)	101.2 (9.9)	101.6 (9.9)	0 (4.1)	–2.6 (3.3)	0.1 (3.8)	–0.4 (–2.8 to 1.9)	–1.7 (–3.9 to 0.6)	1.2 (–0.8 to 3.3)
Hip girth *(cm)*	106.8 (7.1)	106.0 (6.2)	104.5 (6.9)	107.1 (8.7)	104.4 (5.8)	103.9 (7.5)	0.3 (2.8)	–1.6 (1.9)	–0.6 (3)	–0.1 (–2.1 to 1.9)	–0.6 (–2.5 to 1.4)	0.4 (–1.3 to 2.2)
Waist:hip ratio	0.94 (0.09)	0.98 (0.07)	0.97 (0.06)	0.94 (0.07)	0.97 (0.06)	0.98 (0.08)	0.00 (0.03)	–0.01 (0.02)	0.01 (0.03)	–0.00 (–0.03 to 0.02)	–0.01 (–0.04 to 0.01)	0.01 (–0.02 to 0.03)
DXA data												
Total mass *(kg)*	84.4 (14.4)	85.1 (13.7)	79.0 (10.6)	83.9 (14.9)	83.2 (12.4)	80.1 (11.9)	–0.5 (5.4)	–1.9 (4.4)	1.1 (4.9)	–1.8 (–3.3 to –0.4)	–1.2 (–2.5 to 0.2)	–0.7 (–1.9 to 0.6)
Total fat *(kg)*	28.9 (10.5)	29.5 (7.9)	26.9 (7.3)	28.5 (12.1)	27.6 (6.7)	27.3 (8.2)	–0.4 (4.2)	–1.9 (2.50)	0.4 (3.4)	–1.1 (–2.3 to 0.0)	–1.2 (–2.3 to –0.1)	0.1 (–0.9 to 1.1)
Tissue fat *(%)*	35.0 (9.7)	35.7 (6.2)	35.2 (7.3)	34.4 (12.1)	34.3 (6.5)	35.0 (7.5)	–0.6 (4)	–1.4 (2.2)	–0.2 (3.2)	–0.6 (–1.6 to 0.5)	–0.8 (–1.8 to 0.2)	0.2 (–0.7 to 1.2)
Total lean *(kg)*	52.6 (9.8)	52.6 (8.5)	49.3 (8.1)	52.4 (9.9)	52.6 (9.0)	50.0 (8.2)	–0.1 (3.7)	–0.0 (3.0)	0.8 (3.5)	–0.7 (–1.5 to 0.0)	0.0 (–0.7 to 0.7)	–0.7 (–1.4 to –0.1)
BMD *(g/cm^2)*	1.27 (0.16)	1.28 (0.13)	1.27 (0.17)	1.27 (0.15)	1.28 (0.12)	1.26 (0.18)	0 (0.06)	0 (0.04)	–0.01 (0.08)	0.01 (–0.01 to 0.02)	0.01 (–0.01 to 0.02)	0.00 (–0.01 to 0.02)

BMD = bone mineral density, BMI = body mass index, Con = control group, DXA = dual energy x-ray absorptiometry, GEX = gym-based exercise training group, WEX = water-based exercise training group.

[a] Difference between estimated margins of means using general linear mixed model analysis.

3.7 References

1. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al. Physical activity and mortality in patients with stable coronary heart disease. J Am Coll Cardiol. 2017;70:1689–1700.
2. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, et al. Cardiac rehabilitation fitness changes and subsequent survival. Eur Heart J Qual Care Clin Outcomes. 2018;4:173–179.
3. Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107(24):3109–3116.
4. Woodruffe S, Neubeck L, Clark RA, Gray K, Ferry C, Finan J, et al. Australian Cardiovascular Health and Rehabilitation Association (ACRA) core components of cardiovascular disease secondary prevention and cardiac rehabilitation 2014. Heart Lung Circ. 2015;24:430–441.
5. Australian Government Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines and the Australian 24-Hour Movement Guidelines. https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines. Published 2019. Accessed 13/01/2020, 2020.
6. Evenson KR, Butler EN, Rosamond WD. Prevalence of physical activity and sedentary behavior among adults with cardiovascular disease in the United States. J Cardiopulm Rehabil Prev. 2014;34:406–419.
7. Guiraud T, Granger R, Grémeaux V, Bousquet M, Richard L, Soukarie L, et al. Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program. Ann Phys Rehabil Med. 2012;55:312–321.
8. Anderson BK, Phillips MM, Gerald L, DiLillo V, Bittner V. Factors associated with the failure of patients to complete cardiac rehabilitation for medical and nonmedical reasons. J Cardiopulm Rehabil. 2003;23:281–289.
9. Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with heart disease–United States, 2005 and 2007. Morb Mortal Wkly Rep. 2009;58:165–169.
10. Angerås O, Albertsson P, Karason K, Råmunddal T, Matejka G, James S, et al. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2012;34:345–353.
11. Pavy B, Iliou M-C, Vergès-Patois B, Brion R, Monpère C, Carré F, et al. French Society of Cardiology guidelines for cardiac rehabilitation in adults. Arch Cardiovasc Dis. 2012;105:309–328.
12. Becker B. Aquatic therapy: Scientific foundations and clinical rehabilitation applications Am J Phys Med Rehabil. 2009;1:859–872.
13. Scheer AS, Naylor LH, Gan SK, Charlesworth J, Benjanuvatra N, Green DJ, et al. The effects of water-based exercise training in people with type 2 diabetes. Med Sci Sports and Exerc. 2020;52:417–424.
14. Volaklis K, Spassis A, Tomakadis S. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J. 2007;154:560.e561–560.e566.
15. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2:92–98.
16. Carver TE, Christou NV, Andersen RE. In vivo precision of the GE iDXA for the assessment of total body composition and fat distribution in severely obese patients. Obesity. 2013;21:1367–1369.
17. Tokmakidis SP, Spassis AT, Volaklis KA. Training, detraining and retraining effects after a water-based exercise program in patients with coronary artery disease. Cardiology. 2008;111:257–264.
18. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol. 2013;4:863–863.
19. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hoboken: Hoboken: Taylor and Francis; 2013.
20. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J. 2008;156:292–300.

21. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. J Am Coll Cardiol. 2003;42:2139–2143.
22. Haynes A, Naylor LH, Carter HH, Spence AL, Robey E, Cox KL, et al. Land-walking vs. water-walking interventions in older adults: Effects on aerobic fitness. J Sport Health Sci. 2020;9:274–282.
23. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. Int J Sports Med. 2005;26(Suppl 1):S49–S55.
24. Fiogbé E, Ferreira R, Sindorf MAG, Tavares SA, de Souza KP, de Castro Cesar M, et al. Water exercise in coronary artery disease patients, effects on heart rate variability, and body composition: A randomized controlled trial. Physiother Res Int. 2018;23:e1713.
25. Rothney MP, Martin F-P, Xia Y, Beaumont M, Davis C, Ergun D, et al. Precision of GE Lunar iDXA for the measurement of total and regional body composition in nonobese adults. J Clin Densitom. 2012;15:399–404.
26. Hind K, Oldroyd B, Truscott JG. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. Eur J Clin Nutr. 2011;65:140–142.
27. Dordevic AL, Bonham M, Ghasem-Zadeh A, Evans A, Barber E, Day K, et al. Reliability of compartmental body composition measures in weight-stable adults using GE iDXA: Implications for research and practice. Nutrients. 2018;10:1484.
28. Naylor LH, Maslen BA, Cox KL, Spence AL, Robey E, Haynes A, et al. Land- versus water-walking interventions in older adults: Effects on body composition. J Sci Med Sport. 2020;23:164–170.
29. Pinto RS, Gomes N, Radaelli R, Botton CE, Brown LE, Bottaro M. Effect of range of motion on muscle strength and thickness. J Strength Cond Res. 2012;26:2140–2145.
30. Kamiya K, Masuda T, Tanaka S, Hamazaki N, Matsue Y, Mezzani A, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. Am J Med. 2015;128:1212–1219.

Chapter 4. The effects of water-based circuit training exercise on vascular function and blood profiles in patients with stable coronary heart disease

This has been published as a manuscript (short report) in the American Journal of Physiology: Heart and Circulatory Physiology:

Scheer A, Ito Ramos De Oliveira B, Shah A, Jacques A, Chasland LC, Green DJ, and Maiorana AJ. The effects of water-based circuit exercise training on vascular function in people with coronary heart disease. American Journal of Physiology-Heart and Circulatory Physiology 325: H1386-H1393, 2023.

This information is contained in Appendix J.34.

Table 4.1- Attribution statement for Chapter 4

	Conception and design	Acquisition of data and method	Data conditioning	Analysis and statistical method	Interpretation and discussion
Anna Scheer	X	X	X	X	X
Beatriz IR de Oliviera	X				X
Amit Shah	X	X			
Angela Jacques	X			X	X
Lauren Chasland		X			
Daniel J. Green	X	X			X
Andrew Maiorana	X	X	X	X	X

All authors critically revised the manuscript.

For the research paper:

“The effects of water-based circuit exercise training on vascular function in people with coronary heart disease”

I confirm that Anna Scheer developed the concept of the study and contributed to the design of the project. She developed the water-based exercise training program and equipment, she drafted funding applications, completed ethics and governance applications, recruited participants, and collected the data for the study. In consultation with Angela Jacques, she performed the statistical analysis. Anna provided the initial interpretation of the data, the first draft of the manuscript and contributed to manuscript revisions.

Beatriz Ito Ramos de Oliveira

Amit Shah

Lauren Chasland

Angela Jacques

Daniel J. Green

Andrew Maiorana

4.1 Abstract

Impaired endothelial function in people with coronary heart disease (CHD) is associated with increased mortality. Water immersion can increase peripheral artery shear stress which may provide an additional stimulus to the endothelium during exercise. This study compared the effects of water-based circuit exercise training (WEX) and gym-based circuit exercise training (GEX) on vascular function in people with stable CHD. Participants were randomised to 12 wk of WEX (n=20), GEX (n=20) or a control group (usual activities; n=12). Endothelium-dependent flow-mediated dilation (FMD) and glyceryl trinitrate-mediated dilation (GTN) of the brachial artery were assessed pre- and postintervention. FMD increased following WEX [4.0% (3.0-5.1%) to 5.3% (4.1-6.5%); P = 0.016], but was unchanged following GEX [4.9% (3.8-5.9%) to 5.0% (3.8-6.1%); P = 0.822]. There were no between-group differences in the change in FMD and no significant changes in GTN-mediated dilation percentage. Triglycerides decreased following GEX [1.2 mmol.L^{-1} (1.0-1.4 mmol.L^{-1}) to 1.0 mmol.L^{-1} (0.8-1.3 mmol.L^{-1}); P = 0.022], but there were no further differences in lipid profiles. WEX improved endothelial function of the brachial artery in people with stable CHD, suggesting that WEX is an effective alternative to gym-based exercise in people living with CHD, which may specifically address vascular health.

4.1.1 New & Noteworthy

This study found that 12 wk of water-based circuit exercise training was well tolerated and improved vascular endothelial function in people with stable coronary heart disease. However, there was no effect on endothelium independent function. Water-based exercise appears to be an effective alternative to gym-based exercise for people with coronary heart disease, which has specific benefits to vascular health and function.

4.2 Introduction

Coronary heart disease (CHD) is estimated to affect 244 million people globally, and results in approximately 9 million deaths annually (1). Endothelial dysfunction is a cardinal feature of CHD (2, 3), with the degree of impairment linked to disease severity (2).

A recent meta-analysis reported that exercise-based cardiac rehabilitation improves flow mediated dilation (FMD), a measure of endothelial function, in people with CHD (4). Adaptations in endothelial function in response to exercise training are likely the result of repeated exposure to transient increases in shear stress (5, 6), which stimulates the endothelium to release vasoactive substances, including nitric oxide (5). Over time, this may increase the expression of endothelial nitric oxide synthase (eNOS) leading to improved endothelial function (5).

Both hemodynamic and thermal changes during water immersion make water-based exercise an intriguing prospect as an exercise training intervention for improving vascular function. Compared with land-based exercise, exercise in water augments vascular shear stress (7); during immersion, hydrostatic pressure increases venous return from the lower limbs, increasing preload, ventricular volume, and as a consequence, cardiac output (8-10), including in people with heart failure (11). Moreover, water immersion increases limb blood flow, with water temperature appearing to mediate immersion-related peripheral arterial shear stress (7, 12).

Previous studies of water-based exercise have highlighted its potential for vascular benefits. Two to three weeks of intensive water-based exercise training in people with CHD led to increases in flow-mediated dilation (FMD) (13) and plasma nitric oxide metabolites (14), markers of improved endothelial function. Longer duration studies in people with cardiometabolic conditions have shown water-based exercise to increase the concentration of plasma nitric oxide metabolites (15, 16), FMD (15, 17) and microvascular function (15), suggesting favorable effects on the peripheral vasculature. Whilst these extended duration studies in participants with chronic disease are encouraging, there have been no studies >3-wk duration on the effects of water-based exercise on vascular function in people with CHD.

The aim of the current study was to investigate the effects of 12 wk of water-based circuit exercise training (WEX) on vascular function in people with CHD, compared to gym-based circuit exercise training (GEX) and usual care. We hypothesized that 12 wk of WEX

would improve FMD compared to usual care or GEX, without changing endothelium independent artery function.

4.3 Materials and methods

4.3.1 Study Design

This was a parallel group, randomised, controlled trial. Participants were randomized to 12 wk of WEX, or GEX (3 times/ week), or continued their usual activities as a control group. Participants were randomised via block allocation after baseline testing using sealed opaque envelopes. This study was prospectively registered (ACTRN12616000102471).

4.3.2 Participants

Participants were recruited from hospital databases and community advertising. Inclusion criteria were as follows: diagnosed CHD (history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or diagnostic imaging demonstrating ≥50% occlusion of at least 1 coronary artery), prescribed stable medications for ≥ 1mo, and ≥18 yr of age. Exclusion criteria were as follows; heart failure (ejection fraction <45%, or diagnosed diastolic heart failure), recent (≤6 mo) history of angioplasty, bypass graft surgery, or myocardial infarction, an adverse response to baseline exercise testing requiring further investigation, treatment for cancer (≤6 mo), significant impediments to exercise, or blood test results suggesting other substantial health problems. Participants were excluded if they were taking insulin, or were current smokers, due to the potential acute vascular effects. There were no premenopausal participants. All participants provided written, informed consent prior to data collection. This study was approved by Royal Perth Hospital Human Research Ethics Committee (Ref. No. RGS0000002071).

4.3.3 Assessments

Brachial artery FMD (a measure of endothelium-dependent function), and brachial artery glyceryl trinitrate (GTN)-mediated dilation (a measure of endothelium-independent function) were assessed along with blood biochemistry at baseline and within 7 days of the final training session.

4.3.3.1 Brachial artery function

Flow-mediated dilation was assessed before GTN mediated dilation (with ≥ 20 min of rest between tests). A Terason portable ultrasound system (Terason T3200, Teratech, Burlington, MA) was used with a high- resolution linear array transducer (15L4; Terason). Simultaneous B-mode images and Doppler velocities were recorded in a longitudinal plane, proximal to the antecubital fossa during both assessments (18).

Ultrasound assessments occurred in a quiet, temperature- controlled room after participants had fasted for ≥6 h, abstained from moderate to vigorous exercise ≥24 h, and caffeine and alcohol for ≥12 h (18). Participants were assessed after taking their usual medications at the same time of day for baseline and follow up assessments to exclude diurnal variation (18).

Before imaging, participants rested in a supine position for ≥20 min (18). Blood pressure was monitored every 5 min and measurements were undertaken only after blood pressure was stable (<5mmHg variation with previous measurement). The angle of insonation was <60° for Doppler recordings. Ultrasound scans were blinded by a third party for analysis and were analyzed with custom-designed edge detection software that continuously determined arterial diameter and shear rate. This method has been previously described in detail and found to reduce variability compared with manual methods (19).

4.3.3.2 Flow-mediated dilation of the brachial artery

Following a 1- min resting baseline, a blood pressure cuff (Welch Allyn; DS 66 Hand Aneroid Sphygmomanometer) located on the participant's forearm distal to the olecranon process was inflated to 220mmHg. Recording restarted 30 s before cuff deflation and continued for 3 min after cuff deflation (18).

4.3.3.3 Glyceryl trinitrate mediated dilation of the brachial artery

After a 20-min rest from the FMD assessment, a 1-min resting baseline recording was followed by the administration of one 400µg dose of sublingual GTN. Recordings commenced 3 min after the spray and continued for 5 min.

4.3.3.4 Biochemistry

Blood samples were collected from the antecubital fossa after an overnight fast by an accredited laboratory. Full blood picture was taken at baseline, and serum C-reactive

protein, plasma; total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), fibrinogen, total protein, albumin, globulins, bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), sodium, potassium, bicarbonate, urea, creatinine and estimated glomerular filtration rate (eGFR) were assessed at baseline and follow-up. For eGFR, the CKD-EPI algorithm was used, which includes sex, age, and creatinine only.

4.3.4 Exercise training interventions:

For participants to have been classed as having completed the training program, they were required to attend at least 75% of the sessions. The exercise interventions were conducted for 12 wk and have been described in detail previously (20). To summarize, The WEX group trained in a 34.5°C hydrotherapy pool submerged to the level of their xiphoid process and the GEX group trained in a gymnasium. Both modes of exercise were supervised by a physiotherapist or exercise physiologist. Participants in both training groups were prescribed three sessions per week of ~1-h duration per session. This involved a 5-min warm up and cool down of light aerobic activity followed by stretching, plus 45 min of circuit training with alternating aerobic and resistance exercises (45 s of work to 15 s of active recovery). Participants progressed to completing 3 sets of the circuit of 15 exercises per session by the end of week 3 (see [Table 4.5] Supplementary Table 1 for more detailed information on exercise order, http://dx.doi.org/10.6084/m9.figshare.23939754).

For aerobic exercise, target training heart rate was progressed from 50-65% of measured peak heart rate (from a baseline cardiopulmonary exercise test) in weeks 1 and 2, to 60-65% in weeks 3 and 4, 60-70% in weeks 5 and 6, 70-80% in weeks 7 and 8, and 80% from weeks 9-12 (20). Water-based aerobic exercises included high knee walking/jogging on the spot and walking or jogging across the pool. In the gym, walking or jogging on a treadmill and cycle ergometry were prescribed.

Resistance training involved two upper limb (elbow flexion/extension and shoulder abduction/adduction) and five lower limb (hip and knee flexion/extension and hip abduction) stations per circuit (20). Resistance in the pool was applied by drag from custom designed rectangular paddles, involving acrylic plates strapped either side of the limb with hook and loop fastenings or buckles (see [Figure 4.2] Supplemental Fig. S1, http://dx.doi.org/10.6084/m9.figshare.23939652). Movement speed (individualized using waterproof metronomes) and paddle size were modified to increase resistance when participants could maintain the prescribed pace with good form and rating of perceived

exertion (RPE) (Borg) (21) <13 (somewhat hard). Resistance in the gym was applied by a combination of machine stack weights and free weights, starting at ~50% of 1 repetition maximum (RM) in week 1 and progressed when participants could perform 12-15 repetitions with good form over 45 s and RPE <13.

4.3.5 Statistics

Sample size for vascular outcomes was based on changes observed in FMD in people with CHD with circuit training exercise by Walsh et al. (3), FMD increased from 3% to 5.7% (SD of 3%). To detect a mean percent change from 3% to 5.5% (SD of 3%, effect size 0.83) with 80% power (α=0.05) in a repeated measures within and between factors interaction model over 2 timepoints, it was calculated that 11 participants would be needed per group (GPower, version 3, Kiel, Germany). To account for potential participant attrition, a target of 20 participants per training group was set.

Pre-/postdata were analyzed with STATA version 16.1 (StataCorp LLC, TX) using generalized linear mixed models with appropriate links for within-group pre-/postassessment and group-time interactions. Because of the laboratory reporting format, C–reactive protein data were assessed as a binary variable using a mixed-effects logistic model (grouped as <1.0 and ≥1.0mg.L^{-1}) and estimated glomerular filtration rate (eGFR) was assessed with a mixed-effects Tobit model because of a ceiling effect on the data. Total cholesterol was assessed using a log analysis with a γ distribution. $P < 0.05$ was considered statistically significant.

4.4 Results

Baseline assessments were conducted in 60 individuals, with seven excluded for medical reasons and 1 withdrawing from the study. Fifty-two participants were randomized in the study, 20 to WEX, 20 to GEX, and 12 to control. Five participants withdrew from the WEX group (unrelated injury or illness in 2 participants, work or family reasons in 3 participants) and 2 participants withdrew from the GEX group (1 withdrew because of arrhythmia and 1 due to work or family reasons). Fifteen WEX, 18 GEX and 12 control participants completed the study. Baseline characteristics of participants are displayed in Table 4.2. There were no adverse events in the WEX group. One participant, with a history of supraventricular tachycardia, in the GEX group, experienced an episode of supraventricular tachycardia during gym-based training, which resolved after treatment with medication (metoprolol and adenosine).

Table 4.2 Baseline characteristics of participants

Characteristics	WEX	GEX	Control	P Value
n	20	20	12	
Age, (median [range]), *yr*	66.0 [51-77]	70.0 [50-79]	72.5 [63-78]	0.067
Sex, males/females, *n*	15/5	18/2	9/3	0.487
Weight [mean (SD)], kg	83.1 (13.5)	86.4 (13.4)	80.3 (10.4)	0.421
BMI, (median [range]), $kg.m^2$	28.6 (22.5-35.9)	28.8 (22.5-37.6)	26.9 (23.3-35.7)	0.872
Cardiac history, *n (%)*				
Asymptomatic	3 (15)	2 (10)	2 (17)	0.883
Angina (no MI)	5 (25)	7 (35)	5 (42)	0.564
MI	12 (60)	11 (55)	5 (42)	0.583
Years since Dx, (median [range])	3.6 (0.8-15)	2.4 (0.5-29)	5.5 (0.5-18)	0.592
Management, *n (%)*				
Coronary bypass graft	2 (10)	8 (40)	6 (50)	**0.028**
Stent	16 (80)	15 (75)	7 (58)	0.439
Stent and coronary bypass	0 (0)	3 (15)	2 (17)	0.155
Non-invasive treatment	2 (10)	0 (0)	1(8)	0.439
Comorbidities, n (%)				
Hx cancer (excluding minor skin)	3 (15)	5 (25)	2 (17)	0.748
Metabolic (pre/T2DM)	2 (10)	5 (25)	3 (25)	0.487
Hx neurologic (CVA/TIA)	1 (5)	1 (5)	3 (25)	0.189
Other cardiovascular	1 (5)	0 (0)	0 (0)	1.00
Musculoskeletal	16 (80)	10 (50)	9 (75)	0.164
Respiratory	4 (20)	4 (20)	3 (25)	1.00
Medications*, n (%)*				
Antiplatelet/anticoagulant	20 (100)	19 (95)	12 (100)	1.00
Lipid lowering	18 (90)	19 (95)	11 (92)	1.00
Beta blockers	6 (30)	8 (40)	9 (75)	**0.041**
ACE inhibitors	6 (30)	12 (60)	4 (33)	0.186
Angiotensin II receptor blockers	6 (30)	4 (20)	5 (42)	0.462
Calcium channel blockers	4 (20)	3 (15)	3 (25)	0.902
Diuretic	1 (5)	1 (5)	1 (8)	1.00
Glucose lowering	0 (0)	1 (5)	3 (25)	**0.034**
Proton pump inhibitors	7 (35)	5 (25)	5 (42)	0.564

Values are medians [ranges]; means (SD); and number of participants, *n* (%). ACE, angiotensin-converting enzyme; BMI, body mass index; CVA, cerebrovascular accident; Dx, diagnosis; GEX, gym-based circuit exercise-training group; Hx, history of; MI, myocardial infarction; TIA, transient ischemic attack; T2DM, type 2 diabetes mellitus; WEX, water-based circuit exercise-training group. Statistical analysis for categorical variables was conducted using Fisher's exact test, continuous variables with an approximately normal distribution was assessed using a one-way ANOVA (weight), and the Kruskal–Wallis test was used for continuous variables that were not normally distributed (age, body mass index, and time from diagnosis). Boldface indicates significant values.

4.4.1 Flow-mediated dilation

Changes in FMD response are described in Table 4.3. FMD percent change increased by 32.5% following WEX, increasing from 4.0% (3.0-5.1%) to 5.3% (4.1-6.5%), P = 0.016 (Figure 4.1A), however there was no significant within-group difference for GEX (Figure 4.1B), and no significant difference between training groups. There were no changes in baseline diameter or shear rate over time within training groups (Table 4.3). One WEX, two GEX and two control scans were excluded from FMD analysis because of scan quality or motion artefact. Supplementary Table S2
(see http://dx.doi.org/10.6084/m9.figshare.24242434 [Table 4.6 and Table 4.7] provides data from allometric analyses of FMD data.

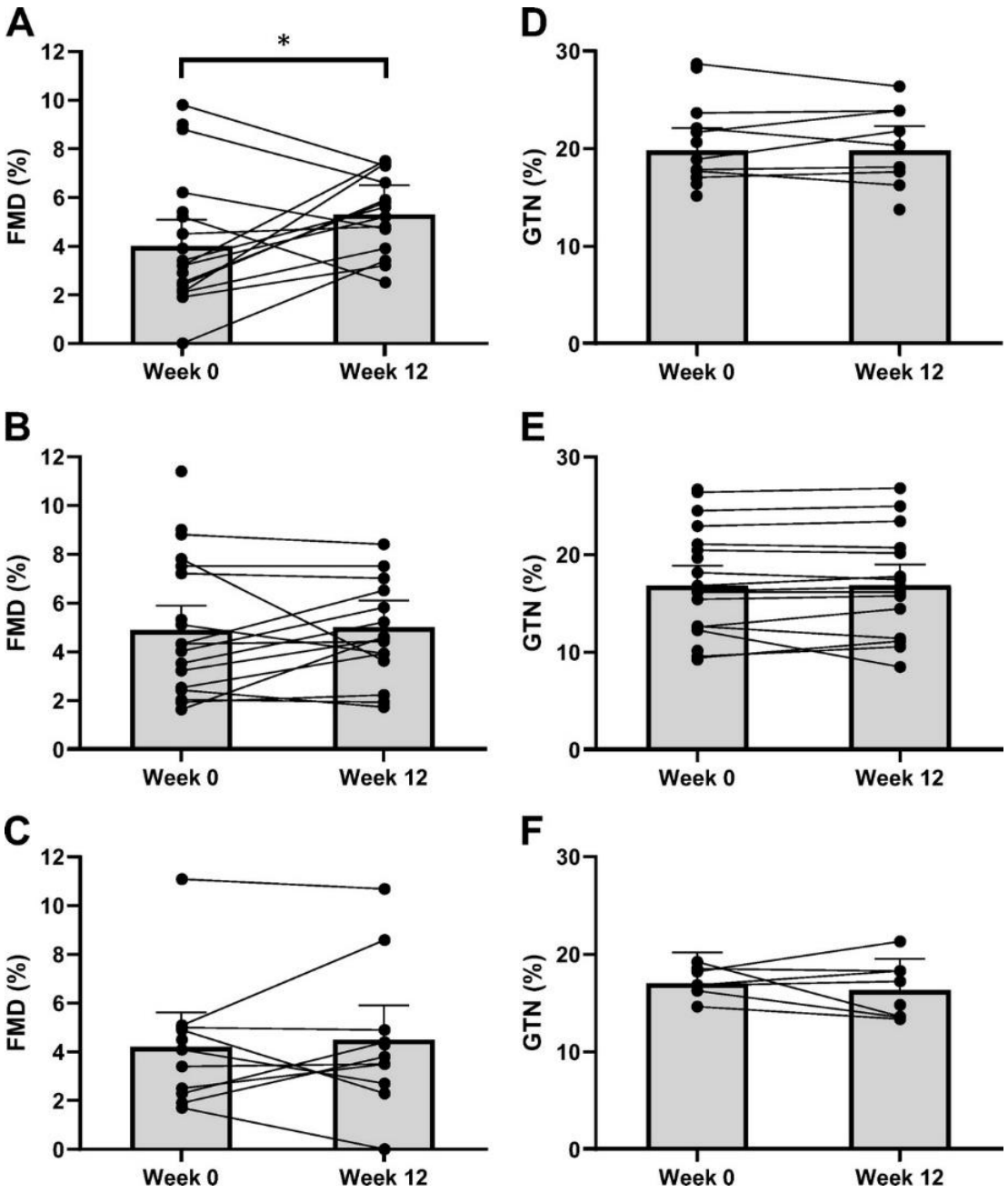


Figure 4.1 Effects of 12 wk of exercise training or control period on vascular function.

Gray bars, estimated means; T bars, upper limits of 95% confidence intervals; black circles, individual data points; black lines, connected paired data. *A–C*: percent change from baseline in FMD at 0 and 12 wk: WEX (*week 0*, *n* = 20; *week 12*, *n* = 14; *A*), GEX (*week 0*, *n* = 20; *week 12*, *n* = 16; *B*), and control (*week 0*, *n* = 11; *week 12*, *n* = 11; *C*). *D–F*: percent change from baseline in GTN-mediated dilation at 0 and 12 wk: WEX (*week 0*, *n* = 14; *week 12*, *n* = 9; *D*), GEX (*week 0*, *n* = 19; *week 12*, *n* = 15; *E*), and control (*week 0*, *n* = 7; *week 12*, *n* = 8; *F*). General linear mixed models used for statistical analysis. **P* = 0.016 between *week 0* and *week 12* WEX measures. No other significant within- or between-group effects over the 12 wk. Exact *P* values described in Table 4.3. FMD, flow-mediated dilation; GEX, gym-based circuit exercise training; GTN, glyceryl trinitrate-mediated dilation; WEX, water-based circuit exercise training.

Table 4.3 Effects of 12 wk of WEX, GEX, or control on vascular function.

	Control			GEX				WEX				
	Week 0	Week12	P1	Week 0	Week 12	P1	P2	Week 0	Week 12	P1	P2	P3
FMD												
n	*11*	*11*		*20*	*16*			*20*	*14*			
Baseline diameter, mm	3.69 (3.39-3.99)	3.78 (3.48-4.08)	0.069	3.94 (3.71-4.17)	3.94 (3.71-4.17)	0.953	0.165	3.73 (3.50-3.96)	3.69 (3.45-3.92)	0.380	0.051	0.496
FMD response, mm	0.15 (0.10-0.20)	0.17 (0.12-0.21)	0.484	0.18 (0.14-0.22)	0.19 (0.15-0.23)	0.681	0.769	0.15 (0.11-0.18)	0.20 (0.16-0.24)	**0.011**	0.277	0.119
FMD response, %	4.2 (2.8-5.6)	4.5 (3.0-5.9)	0.721	4.9 (3.8-5.9)	5.0 (3.8-6.1)	0.822	0.888	4.0 (3.0-5.1)	5.3 (4.1-6.5)	**0.016**	0.204	0.110
Shear rate AUC, s^{-1}, $x10^3$	23.2 (18.3-28.0)	23.7 (18.9-28.5)	0.839	20.2 (16.5-23.9)	19.6 (15.6-23.5)	0.785	0.742	23.7 (20.1-27.3)	22.3 (18.1-26.5)	0.556	0.595	0.816
GTN												
n	*7*	*8*		*19*	*15*			*14*	*9*			
Baseline diameter*, mm	3.74 (3.33-4.16)	3.89 (3.48-4.30)	**0.018**	4.08 (3.81-4.34)	4.09 (3.82-4.35)	0.808	0.070	3.66 (3.36-3.96)	3.64 (3.34-3.95)	0.799	0.057	0.727
Peak diameter, mm	4.38 (3.93-4.82)	4.53 (4.08-4.97)	**0.032**	4.74 (4.46-5.03)	4.77 (4.48-5.06)	0.632	0.133	4.36 (4.04-4.68)	4.35 (4.02-4.68)	0.875	0.093	0.682
GTN response, %	17.0 (13.7-20.2)	16.3 (13.0-19.5)	0.299	16.8 (14.7-18.9)	16.9 (14.8-19.0)	0.833	0.329	19.8 (17.4-22.1)	19.8 (17.3-22.3)	0.929	0.411	0.958

Values are means (95% confidence intervals); *n*, number of scans analyzed for that group and week. AUC, area under the curve; FMD, flow-mediated dilation; GTN, glyceryl trinitrate-mediated dilation; GEX, gym-based circuit exercise-training group; *P1*, *P* value for analysis of *week 0* vs. *week 12*; *P2*, *P* value vs. change in control group; *P3*, *P* value for change in WEX vs. change in GEX; WEX, water-based circuit exercise-training group. **P* < 0.05 at *week 0* between WEX and GEX. General linear mixed models used for statistical analysis. Boldface indicates significant values.

4.4.2 Glyceryl trinitrate mediated dilation

Changes in GTN mediated dilation are described in Table 4.3. There were no significant within- or between-group changes in endothelium independent function measured by percentage change in GTN-mediated dilation (Table 4.3, Figure 4.1 D-F). Numbers of scans included in the analysis are outlined in Table 4.3, GTN was not assessed in three control and five WEX participants during one or more visits because of medical contraindications. One participant in the WEX group declined GTN. Four control, two WEX, and three GEX scans were excluded because of scan quality or motion artefact. Two participants in the WEX group did not receive a full dose of GTN at baseline assessment because of dispenser malfunction.

4.4.3 Blood biochemistry

Blood parameters remained relatively stable across the 12-wk period (Table 4.4). While there were no differences between groups in total cholesterol, triglycerides reduced by 17% with GEX ($P = 0.022$). Fibrinogen was 5% lower after GEX ($P = 0.012$ vs control, $P = 0.048$ vs WEX). There was no change in C-reactive protein when assessed as a binary variable using a mixed-effects logistic model.

Table 4.4 Effects of 12 wk of WEX, GEX, or control on blood biochemistry.

	Control			GEX				WEX				
	Week 0	Week12	P1	Week 0	Week 12	P1	P2	Week 0	Week 12	P1	P2	P3
n	*12*	*12*		*20**	*18*			*19*	*15*			
Total Chol§,mmol.L^{-1}	3.9 (3.4-4.4)	3.9 (3.3-4.4)	0.855	3.9 (3.5-4.3)	3.8 (3.4-4.2)	0.562	0.612	4.1 (3.7-4.5)	4.0 (3.6-4.5)	0.497	0.557	0.914
HDL, mmol.L^{-1}	1.3 (1.1-1.4)	1.3 (1.1-1.5)	0.584	1.3 (1.1-1.4)	1.3 (1.1-1.4)	0.453	0.961	1.4 (1.2-1.5)	1.3 (1.2-1.5)	0.840	0.587	0.512
LDL, mmol.L^{-1}	2.0 (1.6-2.4)	2.0 (1.6-2.4)	0.945	2.1 (1.8-2.4)	2.0 (1.7-2.3)	0.749	0.799	2.2 (1.9-2.6)	2.2 (1.9-2.5)	0.585	0.679	0.853
Triglycerides, mmol.L^{-1}	1.3 (1.0-1.6)	1.4 (1.1-1.7)	0.567	1.2 (1.0-1.4)	1.0 (0.8-1.3)	**0.022**	0.059	1.2 (0.9-1.4)	1.1 (0.9-1.4)	0.630	0.454	0.232
Fibrinogen, g.L^{-1}	3.6 (3.3-3.9)	3.8 (3.4-4.1)	0.084	3.7 (3.4-4.0)	3.5 (3.3-3.8)	0.067	**0.012**	3.5 (3.2-3.7)	3.6 (3.3-3.8)	0.321	0.526	**0.048**
Creatinine, µmol.L^{-1}	84 (74-93)	81 (71-90)	0.174	90 (82-97)	89 (81-96)	0.680	0.427	81 (73-88)	80 (73-88)	0.953	0.328	0.814
eGFR†, mL.min^{-1} .1.73m^2	74 (66-81)	77 (70-85)	0.108	76 (70-82)	77 (71-83)	0.511	0.389	81 (75-87)	80 (74-86)	0.434	0.083	0.308
ALT, U.L^{-1}	29 (21-37)	29 (21-37)	0.968	35 (29-41)	32 (25-38)	**0.039**	0.204	34 (27-40)	32 (26-39)	0.509	0.683	0.365
ALK, U.L^{-1}	70 (60-81)	74 (64-85)	**0.029**	72 (63-80)	69 (61-77)	0.155	**0.010**	71 (63-79)	69 (61-78)	0.380	**0.027**	0.755
GGT, U.L^{-1}	27 (13-41)	23 (9-36)	0.172	32 (21-43)	32 (21-43)	0.945	0.270	37 (26-48)	38 (27-49)	0.798	0.234	0.887
Total protein, g.L^{-1}	71 (69-72)	72 (70-74)	0.193	73 (71-75)	72 (70-73)	0.110	**0.044**	72 (70-74)	72 (70-74)	0.943	0.304	0.302
Albumin, g.L^{-1}	42 (40-43)	42 (40-43)	0.869	43 (42-44)	42 (41-43)	0.263	0.405	42 (41-43)	42 (41-43)	0.529	0.589	0.769
Globulin, g.L^{-1}	29 (28-31)	30 (29-31)	0.052	30 (29-31)	29 (28-31)	0.106	**0.012**	30 (28-31)	30 (29-31)	0.726	0.221	0.176
Bilirubin, g.L^{-1}	13 (10-16)	12 (9-15)	0.652	13 (10-15)	13 (10-15)	0.977	0.713	14 (11-16)	15 (12-18)	0.266	0.283	0.424

Values are means (95% confidence intervals); n, number analyzed. ALK, alkaline phosphatase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transferase; GEX, gym-based circuit exercise-training group; HDL, high-density lipoprotein; LDL, low-density lipoprotein; P1, P value for analysis of week 0 vs. week 12; P2, P value vs. change in control group; P3, P value for change in WEX vs. change in GEX; Total Chol, total cholesterol; Total protein, total plasma protein; WEX, water-based circuit exercise-training group. *n = 19 for GEX week 0 total cholesterol, LDL, triglycerides, and fibrinogen. §Log analysis with γ-distribution. †Tobit analysis used. General linear mixed models used for statistical analysis, unless otherwise specified. Boldface indicates significant values.

4.5 Discussion

This is the first study, to our knowledge, to investigate the effects of water-based circuit exercise training on vascular endothelial function in people with stable CHD. The increase in the percent change in brachial artery FMD from baseline of 1.3%, observed with WEX, represented a 32.5% relative improvement from the pretraining value. However, there was no significant difference in FMD following the gym-based intervention at a matched duration and intensity. These findings highlight the vascular benefits of water-based exercise and underscore the potential benefits of WEX in the secondary prevention of cardiovascular events.

Mechanistically, repetitive bouts of increased shear stress have been implicated in enhancing endothelial nitric oxide synthase (eNOS) expression and phosphorylation (5) and in improving endothelial function with land-based training (6). The unique cardiovascular hemodynamics associated with water immersion may further mediate vascular adaptations to WEX. Upright water immersion causes hydrostatic pressure on the lower limbs to enhance venous return and cardiac blood volume, increasing cardiac output (9, 10) and has been found to increase arm blood flow at rest (8, 22). Consistent with these observations, a recent study observed increased brachial artery antegrade shear during water-based cycling (7) lending credence to the hypothesis that augmented shear stress observed in response to acute exercise may be a mechanism for the observed increase in FMD seen with WEX in this study. In addition to the direct hemodynamic effect of water immersion and exercise, water temperature also appears to mediate the vascular response. Brachial artery shear rate is reduced with immersion in 30°C water, with reductions in antegrade shear and increases in retrograde shear (12). This pattern of shear may be due to increased activation of the sympathetic nervous system and reduced skin blood flow observed at this skin temperature (23). Conversely, increased brachial artery diameter and brachial and forearm blood flow have been observed with 34.5 °C immersion (8, 22), and stepwise increases in antegrade shear stress occurred during immersed cycling at 32°C and 38°C (7). Furthermore, immersion in 34°C water has been found to reduce sympathetic nervous system activity (24), which is heightened in people with cardiovascular disease and can counteract endothelium-dependent vasodilation (25).

The hydrostatic and temperature related effects of immersion may have contributed to the discrepancies in the WEX and GEX findings. Some research has indicated a ‘threshold’ effect for shear stress may exist for eliciting significant brachial artery dilation

acutely (26), which may not have been achieved for the brachial artery in the predominantly lower limb-based GEX program without the augmentation from water immersion. In support of the threshold theory, a recent trial by Taylor et al. (27) in people with CHD found moderate intensity exercise failed to improve FMD in people with CHD, while high intensity interval training significantly increased FMD (+1.5%, 95% CI 0.9 to 2.1). High intensity exercise elicits a greater increase in postexercise brachial artery shear stress than moderate intensity exercise (28). Further research is needed to determine the acute changes in shear with immersed circuit training exercises.

The improvement in FMD with WEX observed in the current study is supported by previous short duration, water-based exercise studies in inpatients with CHD (13, 14). Vasić et al. (13) reported that 2 wk of moderate intensity exercise (60%–80% of peak heart rate) performed for 30 min twice daily, 6 days/wk improved FMD in people who had experienced an acute coronary syndrome in the past 4 wk, with no difference between land- and water-based exercise. In contrast, Mourot et al. (14) observed an increase in plasma nitrate (metabolite of nitric oxide, associated with endothelial function) with water- but not land-based training from twice daily sessions, 5 days/wk for 3 wk. Although these short-duration studies show promising results, the programs would be difficult to sustain in the intensive format as an ongoing, regular exercise program. Findings from the current study suggest a longer duration WEX program, involving a lower training frequency, is efficacious for improving endothelial function in people with stable CHD.

Although this is the first study of a WEX program >3 wk to evaluate the effects on endothelial function in people with CHD, longer duration studies have been conducted in other populations. In healthy older adults, a randomized, controlled trial by our group found 24 wk of land-based walking increased FMD, but water walking did not (29). This conflicting finding may reflect the different training stimulus. In the current study, we combined aerobic and resistance training, which may alter the shear stress pattern [proposed to mediate vascular function adaptations (5)], or disparities may be due to differences in vascular health between participants in the two studies (known atherosclerotic disease vs. no significant health issues), or differences in water temperature (28°C–30°C vs. 34.5°C). Results more consistent with the current study were reported in healthy, middle-aged adults who completed a 12-wk water (33°C) or land-based treadmill program. This study observed a 31% increase in eNOS expression following water-based exercise, but no change with land-based training (30).

While the effects of water-based training on vascular function varied in healthy individuals, people with cardiometabolic conditions may obtain greater benefits from WEX. Studies in people with type 2 diabetes (15, 17), peripheral arterial disease (31), and resistant hypertension (16) all found improvement in markers of vascular function with water-based training, highlighting the potential for water exercise to positively impact vascular health in those most at risk.

There were no significant changes in GTN-mediated dilation with either form of exercise training in the current study. This differs from Vasić et al. (13), who found small increases in GTN-mediated vasodilation with short-term water or land-based training programs in people with CHD. The contrasting findings may reflect the recency of participants' coronary event/intervention (<4 wk), lower GTN-mediated dilation at baseline (10%–11% vs. 16%–20%), or Vasić et al.'s more intensive training intervention. Similar to the current study, 24 wk of land or water walking in healthy older adults revealed no changes in GTN-mediated dilation (29). In addition, a meta-analysis found no change in GTN-mediated dilation with exercise-based rehabilitation in people with CHD (4).

Lipid profiles were relatively stable during this study. Total, HDL, and LDL cholesterol were unchanged in either training group. Triglycerides significantly decreased by 17% with GEX, compared with an 8% increase in the control group. Comparatively, Volaklis et al. (32) observed 10% and 12% reductions in triglycerides with water and gym-based training, respectively. Triglyceride improvement may be particularly relevant for secondary prevention in people with CHD, as an elevated risk of recurrent atherosclerotic events has been observed in people with elevated triglyceride levels (33).

Evaluating the efficacy of alternative exercise modalities, such as WEX, for people with CHD is important to increase exercise variety and choice. Along with the improvement in FMD found in this study, we found this program significantly improves aerobic capacity [peak oxygen consumption ($\dot{V}O_{2peak}$)], leg strength, and body fat in people with CHD (20), highlighting a range of potential health benefits of WEX. Ultimately, a broad range of exercise options are important for inclusivity in the context of cardiac rehabilitation and secondary prevention.

4.5.1 Study limitations

There are several limitations of this study that warrant highlighting. First, participants were ≥6 mo post coronary event or intervention and clinically stable. Although this reflects

a large proportion of people living with CHD in the community, the safety and efficacy of WEX in people who have experienced a recent coronary event requires further investigation. Second, participants taking insulin were excluded from this study, as acute changes in insulin levels are known to affect FMD measures (34). Accordingly, the results cannot be generalized to these subgroups of people with CHD.

4.5.2 Conclusion

Twelve weeks of WEX improved FMD in people with stable CHD. The observed benefits of water-based exercise for vascular health and function highlight this mode of exercise as an effective training option for people with stable CHD, which may improve inclusivity and access to exercise, especially for those who have historically opted out of traditional gym-based exercise.

4.6 Supplementary material

Table 4.5 Supplementary Table 1

Supplementary Table 1- Exercise circuit for WEX and GEX groups.

Participants completing 3 circuits per session (after 3 weeks).

To ensure even muscle activity over the program, the starting circuit was alternated each session e.g. Session 1 was ABA, Session 2 was BAB (so 3x 'A' and 3x 'B' circuits every 2 sessions).

Station	GEX- Circuit A	GEX- Circuit B
1	Treadmill walk or jog	Treadmill walk or jog
2	Bilateral knee extension	Bilateral knee extension
3	Cycle ergometer	Cycle ergometer
4	Bilateral hamstrings	Bilateral hamstrings
5	Treadmill walk or jog	Treadmill walk or jog
6	Shoulder adduction	Shoulder abduction
7	Cycle ergometer	Cycle ergometer
8	Right hip flexion	Right hip extension
9	Treadmill walk or jog	Treadmill walk or jog
10	Left hip flexion	Left hip extension
11	Cycle ergometer	Cycle ergometer
12	Bilateral elbow flexion	Bilateral elbow extension
13	Treadmill walk or jog	Treadmill walk or jog
14	Right hip abduction	Left hip abduction
15	Cycle ergometer	Cycle ergometer

Station	WEX- Circuit A	WEX- Circuit B
1	High knees	High knees
2	Right knee flexion/ extension	Right knee flexion/ extension
3	Walking or jogging	Walking or jogging
4	Left knee flexion/ extension	Left knee flexion/ extension
5	High knees	High knees
6	Bilateral shoulder abduction/adduction	Bilateral shoulder abduction/adduction
7	Walking or jogging	Walking or jogging
8	Right hip flexion/ extension	Right hip flexion/ extension
9	High knees	High knees
10	Left hip flexion/ extension	Left hip flexion/ extension
11	Walking or jogging	Walking or jogging
12	Elbow flexion/ extension	Elbow flexion/ extension
13	High knees	High knees
14	Right hip abduction	Left hip abduction
15	Walking or jogging	Walking or jogging

This is available through the link: http://dx.doi.org/10.6084/m9.figshare.23939754

Supplementary Figure 1 - Resistance paddle design.

Supp.1A is a side on view of the paddle applied in the direction for hip/knee flexion and extension movements.

Supp. 1B is the front on view of the paddle applied for the same movements.

Acrylic sheets ranged from 15 x 20cm (smallest upper limb size) through to 30 x 35cm (largest lower limb size).

Supp. 1A.

Supp. 1B.

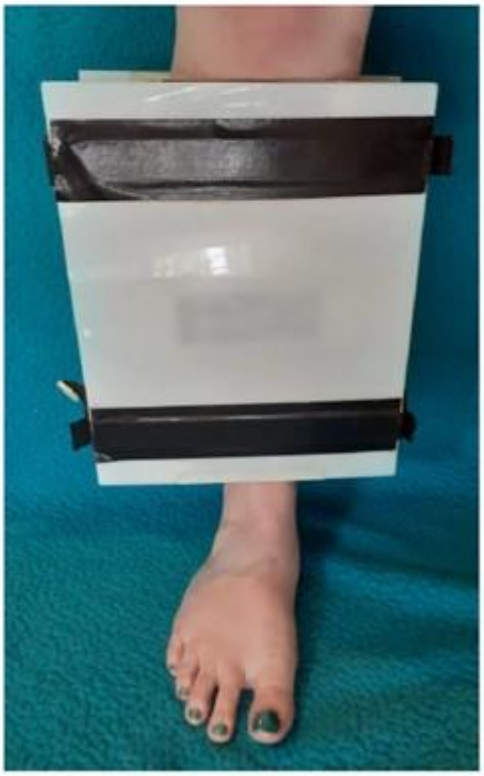


Figure 4.2 Supplementary Figure 1

This is available through the link: http://dx.doi.org/10.6084/m9.figshare.23939652

Table 4.6 Supplementary Table 2A

Supplementary Table 2A. Effects of 12 weeks of WEX, GEX or control on vascular function - allometrically scaled data. Data are estimated mean (95% CI).

	CON			GEX				WEX				
	Week 0	Week12	p1	Week 0	Week 12	p1	p2	Week 0	Week 12	p1	p2	p3
FMD	*n=11*	*n=11*		*n=20*	*n=16*			*n=20*	*n=14*			
Baseline diameter (mm)	3.69 (3.39-3.99)	3.78 (3.48-4.08)	0.069	3.94 (3.71-4.17)	3.94 (3.71-4.17)	0.953	0.165	3.73 (3.50-3.96)	3.69 (3.45-3.92)	0.380	0.051	0.496
FMD response (mm)	0.15 (0.10-0.20)	0.17 (0.12-0.21)	0.484	0.18 (0.14-0.22)	0.19 (0.15-0.23)	0.681	0.769	0.15 (0.11-0.18)	0.20 (0.16-0.24)	**0.011**	0.277	0.119
FMD response (%)	4.2 (2.8-5.6)	4.5 (3.0-5.9)	0.721	4.9 (3.8-5.9)	5.0 (3.8-6.1)	0.822	0.888	4.0 (3.0-5.1)	5.3 (4.1-6.5)	**0.016**	0.204	0.110
Allometrically scaled FMD response (%)^#	4.1 (2.9-5.2)	4.2 (3.0-5.4)	0.906	5.1 (4.2-6.0)	4.8 (3.8-5.9)	0.704	0.752	3.7 (2.8-4.6)	4.8 (3.7-5.8)	0.109	0.376	0.150
IAS (all, cohort exponent)	1.132 (1.119-1.146)	1.135 (1.121-1.149)	0.715	1.142 (1.132-1.152)	1.143 (1.132-1.154)	0.861	0.859	1.129 (1.119-1.140)	1.143 (1.131-1.155)	**0.013**	0.187	0.090
IAS (all, group exponent)§!^	1.127 (1.114-1.140)	1.129 (1.116-1.142)	0.745	1.235 (1.225-1.245)	1.236 (1.225-1.247)	0.853	0.899	1.082 (1.072-1.091)	1.095 (1.084-1.107)	**0.009**	0.155	0.077
IAS (paired, cohort exponent)	1.122 (1.108-1.136)	1.129 (1.115-1.143)	0.284	1.129 (1.118-1.141)	1.133 (1.122-1.144)	0.468	0.697	1.121 (1.109-1.133)	1.134 (1.122-1.146)	**0.014**	0.443	0.194
IAS (paired, group exponent)§!^	1.126 (1.112-1.140)	1.129 (1.115-1.143)	0.650	1.1975 (1.187-1.208)	1.200 (1.189-1.211)	0.632	0.953	1.081 (1.069-1.092)	1.095 (1.083-1.107)	**0.010**	0.192	0.123
Shear rate AUC (s^{-1}, $x10^3$)	23.2 (18.3-28.0)	23.7 (18.9-28.5)	0.839	20.2 (16.5-23.9)	19.6 (15.6-23.5)	0.785	0.742	23.7 (20.1-27.3)	22.3 (18.1-26.5)	0.556	0.595	0.816

CON, control group; GEX, gym-based circuit exercise training group; WEX, water-based circuit exercise training group; IAS, individual data point allometric scaling (peak diameter/base diameter^{exponent}); all, all data points used in exponent calculation and analysis; paired, data with pre-post paired points included in exponent calculation and analysis; exponent, the slope of the regression of the natural log of baseline and peak diameters (the allometric exponent); raw, no exponent in calculation (i.e. peak/base diameter); cohort exponent, calculated from all participants and timepoints in study; group exponent, calculated from each group for pooled timepoints; group and week exponent, calculated from each group at each time point; p1, p value for analysis of week 0 versus week 12; p2, p value vs change in control group; p3, p value for change in WEX vs change in GEX; n, number of scans analyzed for that group and week; FMD, flow mediated dilation; GTN, glyceryl trinitrate mediated dilation; AUC, area under the curve; ^ $p<0.05$ at week 0 between WEX and GEX; ! $p<0.05$ at week 0 between GEX and CON; § = $p<0.05$ at week 0 between WEX and CON, # *Analysis- mixed effects general linear model (log link) with group and time interaction and a fixed covariate of the natural log of baseline, estimated means back-transformed. Other analyses- g*eneral linear mixed models.

Table 4.7 Supplementary Table 2B

Common slope of logarithmically transformed baseline and peak diameter.

	All data		Paired data	
Group	**Slope**	**95% CI**	**Slope**	**95% CI**
Cohort	0.94	(0.91-0.97)	0.94	(0.91-0.97)
CON	0.94	(0.85-1.03)	0.94	(0.84-1.03)
GEX	0.88	(0.84-0.93)	0.90	(0.86-0.94)
WEX	0.97	(0.92-1.01)	0.97	(0.92-1.02)
CON Week 0	0.91	(0.80-1.02)	0.90	(0.77-1.02)
CON Week 12	0.98	(0.81-1.14)	0.98	(0.80-1.16)
GEX Week 0	0.86	(0.80-0.92)	0.89	(0.83-0.96)
GEX Week 12	0.91	(0.85-0.98)	0.91	(0.85-0.98)
WEX Week 0	0.96	(0.89-1.02)	0.96	(0.88-1.05)
WEX Week 12	0.98	(0.92-1.04)	0.98	(0.92-1.04)

Cohort, all participants from all groups at all timepoints; CON, control group; GEX, gym-based circuit exercise training group; WEX, water-based circuit exercise training group. Analysis: linear regression of natural log of baseline and peak diameters by group and by group and week.

Supplementary table 2A and 2B link: http://dx.doi.org/10.6084/m9.figshare.24242434

4.7 References

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, et al. Heart disease and stroke statistics—2022 update: A report from the American Heart Association. Circulation 145: e153-e639, 2022.
2. Arakawa K, Ohno M, Horii M, Ishigami T, Kimura K, and Tamura K. Impact of flow-mediated dilatation and coronary calcification in providing complementary information on the severity of coronary artery disease. Atherosclerosis 267: 146-152, 2017.
3. Walsh J, Bilsborough W, Maiorana A, Best M, O'Driscoll G, Taylor R, and Green D. Exercise training improves conduit vessel function in patients with coronary artery disease. J Appl Physiol 95: 20-25, 2003.
4. Manresa-Rocamora A, Ribeiro F, Casanova-Lizón A, Flatt AA, Sarabia JM, and Moya-Ramón M. Cardiac rehabilitation improves endothelial function in coronary artery disease patients. Int J Sports Med 2022.
5. Green DJ, Hopman MTE, Padilla J, Laughlin MH, and Thijssen DHJ. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. Physiol Rev 97: 495-528, 2017.
6. Tinken T, Thijssen D, Hopkins N, Dawson E, Cable T, and Green D. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension 55: 312-318, 2010.
7. Carter HH, Cheng JL, MacDonald MJ, Pienaar O, Coleman A, Naylor LH, and Green DJ. The effects of exercise during water immersion on arterial function in humans. Am J Physiol Regul Integr Comp Physiol 324: R568-R573, 2023.
8. Ayme K, Gavarry O, Rossi P, Desruelle A-V, Regnard J, and Boussuges A. Effect of head-out water immersion on vascular function in healthy subjects. Appl Physiol Nutr Metab 39: 425-431, 2014.
9. Christie J, Sheldahl L, Tristani F, Wann L, Sagar K, Levandoski S, Ptacin M, et al. Cardiovascular regulation during head- out water immersion exercise. J Appl Physiol 69: 657-664, 1990.
10. Gabrielsen A, Warberg J, Christensen N, Bie P, Stadeager C, Pump B, and Norsk P. Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am J Physiol Regul Integr Comp Physiol 278: 1583-1588, 2000.
11. Grüner Sveälv B, Cider A, Täng MS, Angwald E, Kardassis D, and Andersson B. Benefit of warm water immersion on biventricular function in patients with chronic heart failure. Cardiovasc Ultrasound 7: 33, 2009.
12. Carter HH, Spence AL, Ainslie PN, Pugh CJA, Naylor LH, and Green DJ. Differential impact of water immersion on arterial blood flow and shear stress in the carotid and brachial arteries of humans. Physiol Rep 5: e13285-e13285, 2017.
13. Vasić D, Novaković M, Božič Mijovski M, Barbič Žagar B, and Jug B. Short-term water- and land-based exercise training comparably improve exercise capacity and vascular function in patients after a recent coronary event: A pilot randomized controlled trial. Front Physiol 10: 2019.
14. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Training-induced increase in nitric oxide metabolites in chronic heart failure and coronary artery disease: an extra benefit of water-based exercises? Eur J Cardiovasc Prev Rehabil 16: 215-221, 2009.
15. Suntraluck S, Tanaka H, and Suksom D. The relative efficacy of land-based and water-based exercise training on macro- and microvascular functions in older patients with type 2 diabetes. J Aging Phys Act 25: 446, 2017.
16. Cruz LGdB, Bocchi EA, Grassi G, and Guimaraes GV. Neurohumoral and endothelial responses to heated water-based exercise in resistant hypertensive patients. Circ J 81: 339-345, 2017.
17. Scheer AS, Naylor LH, Gan SK, Charlesworth J, Benjanuvatra N, Green DJ, and Maiorana AJ. The effects of water-based exercise training in people with type 2 diabetes. Med Sci Sports Exerc 52: 417-424, 2020.
18. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, Zock PL, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J 40: 2534-2547, 2019.
19. Woodman R, Playford D, Watts G, Cheetham C, Reed C, Taylor R, Puddey I, et al. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. J Appl Physiol 91: 929-937, 2001.

20. Scheer A, Shah A, Ito Ramos de Oliveira B, Moreno-Suarez I, Jacques A, Green D, and Maiorana A. Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial. J Physiother 67: 284-290, 2021.
21. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14: 377-381, 1982.
22. Gabrielsen, VidebÆk, Johansen, Warberg, Christensen, Pump, and Norsk. Forearm vascular and neuroendocrine responses to graded water immersion in humans. Acta Physiol Scand 169: 87-94, 2000.
23. Greaney JL, Kenney WL, and Alexander LM. Neurovascular mechanisms underlying augmented cold-induced reflex cutaneous vasoconstriction in human hypertension. J Physiol 595: 1687-1698, 2017.
24. Mano T, Iwase S, Saito M, Koga I, Abe H, Inamura K, and Matsukawa T. Neural and humoral controlling mechanisms of cardiovascular functions in man under weightlessness simulated by water immersion. Acta Astronaut 23: 31-33, 1991.
25. Amiya E, Watanabe M, and Komuro I. The relationship between vascular function and the autonomic nervous system. Ann Vasc Dis 7: 109-119, 2014.
26. Wray DW, Witman MA, Ives SJ, McDaniel J, Fjeldstad AS, Trinity JD, Conklin JD, et al. Progressive handgrip exercise: evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. Am J Physiol Heart Circ Physiol 300: H1101-1107, 2011.
27. Taylor JL, Keating SE, Holland DJ, Green DJ, Coombes JS, and Bailey TG. Comparison of high intensity interval training with standard cardiac rehabilitation on vascular function. Scand J Med Sci Sports 32: 512-520, 2022.
28. Padilla J, Harris RA, Rink LD, and Wallace JP. Characterization of the brachial artery shear stress following walking exercise. Vasc Med 13: 105-111, 2008.
29. Haynes A, Naylor LH, Spence AL, Robey E, Cox KL, Maslen BA, Lautenschlager NT, et al. Effects of land- vs water-walking interventions on vascular function in older adults. Med Sci Sports Exerc 53: 83-89, 2021.
30. Lambert BS, Greene NP, Carradine AT, Joubert DP, Fluckey JD, and Riechman SE. Aquatic treadmill training reduces blood pressure reactivity to physical stress. Med Sci Sports Exerc 46: 809-816, 2014.
31. Park S-Y, Wong A, Son W-M, and Pekas EJ. Effects of heated water-based versus land-based exercise training on vascular function in individuals with peripheral artery disease. J Appl Physiol 128: 565-575, 2020.
32. Volaklis K, Spassis A, and Tomakadis S. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J 154: 560.e561-560.e566, 2007.
33. Matsumoto I, Moriya S, Kurozumi M, Namba T, and Takagi Y. Simultaneous evaluation of fatty acid and triglycerides after percutaneous coronary intervention. J Cardiol 80: 149-154, 2022.
34. Campia U, Sullivan G, Bryant MB, Waclawiw MA, Quon MJ, and Panza JA. Insulin impairs endothelium-dependent vasodilation independent of insulin sensitivity or lipid profile. Am J Physiol Heart Circ Physiol 286: H76-H82, 2004.

Chapter 5. The effects of water-based circuit training exercise on cerebrovascular function in patients with stable coronary heart disease

Table 5.1 Attribution statement for Chapter 5

	Conception and design	Acquisition of data and method	Data conditioning	Analysis and statistical method	Interpretation and discussion
Anna Scheer	X	X	X	X	X
Andrew Maiorana	X	X		X	X
Kurt Smith	X	X			X
Howard Carter		X			X
Angela Jacques				X	
Hannah J Thomas		X			
Beatriz IR de Oliviera	X				
Daniel J. Green	X	X			X

All authors critically revised the manuscript.

This chapter has been submitted to the Journal of Physiology as a manuscript for consideration.

For the research manuscript:

“The effects of water-based circuit training exercise on cerebrovascular function in people with stable coronary heart disease”

I confirm that Anna Scheer developed the concept of the study and contributed to the design of the project. She developed the water-based exercise training program and equipment, she drafted funding applications, completed ethics and governance applications, recruited participants, and collected the data for the study. In consultation with Angela Jacques, she performed the statistical analysis. Anna provided the initial interpretation of the data, the first draft of the manuscript and contributed to manuscript revisions.

Andrew Maiorana

Kurt Smith

Howard Carter

Angela Jacques

Hannah J Thomas

Beatriz Ito Ramos de Oliveira

Daniel J. Green

5.1 Abstract

Coronary heart disease (CHD) has been associated with impaired cerebral perfusion and changes in cognition and brain structure. The increase in cerebral blood velocity (CBv) observed during water-based exercise presents a potential mechanism for improving cerebrovascular outcomes in people with CHD. Fifty-two participants with stable CHD were randomised to three, 1-hour sessions/week of either water-based circuit training exercise (WEX, n=20), gym-based circuit training exercise (GEX, n=20), or usual activities control (n=12), over 12 weeks. Transcranial Doppler ultrasound was used to assess CBv and photoplethysmography assessed continuous blood pressure at rest, during neurovascular coupling (NVC), and during repeated mini squat stands (at 0.167Hz). Transfer function analysis was used to assess dynamic cerebral autoregulation (dCA). Eleven WEX, 14 GEX, and 10 control participants completed at least one cerebrovascular/ blood pressure assessment at baseline and follow-up. Compared to GEX, WEX precipitated a reduction in dCA very low frequency (VLF) gain and normalised gain at rest ($p=0.010$ and $p=0.047$) and during squat stands ($p=0.003$ and $p<0.001$). The mean difference in posterior cerebral artery velocity NVC response between WEX and GEX over the program did not reach statistical significance (5-10 seconds: 3.7cm.s^{-1}, $p=0.067$; 10-15 seconds: 3.8cm.s^{-1}, $p=0.088$). There were no effects of training on resting CBv. The directionally different adaptations in the VLF spectrum gain and normalised gain we observed between WEX and GEX suggest that water-based exercise may be a beneficial physiological approach for improving cerebrovascular perfusion-pressure regulation and supports the prescription of WEX for improving cerebrovascular outcomes in people with CHD.

5.2 Introduction

Lower body water immersion in the upright posture induces changes in cardiovascular and neural responses and reflexes, including increases in cerebral blood flow (1, 2), some aspects of cognitive function (3), and a reduction in sympathetic nervous system activity (4). Hydrostatic pressure is an important factor in these physiological changes, driving increases in venous return, central blood volume, cardiac preload and output (5-7). Concomitant increases in cerebral blood velocities (CBv) (1, 2) and cortical oxygenated haemoglobin (8, 9) have also been observed. The associated increase in perfusion may have cerebrovascular benefits, as improvements in cognitive function have been observed during water immersion in older (3) and younger (10, 11) individuals.

Upregulation of CBv may be particularly beneficial for patients with coronary heart disease (CHD), given that impaired cerebral perfusion (12, 13) and cognitive function (14) have been observed in these patients, and low cerebral perfusion has been associated with impaired cognitive function across a range of cardiovascular conditions (15). These maladaptations may be progressive, with cognitive function found to decline over time in people with CHD (16). A recent review by Ovsenik *et al.* (2021) highlighted the need for further research into cerebral blood flow assessment for early detection of the risk of cognitive decline in people with heart failure (17).

Exercise has been identified as a potential strategy to improve cerebral function (18, 19), and cognition (19, 20) in older adults. Furthermore, correlations between aerobic fitness (VO_{2peak}) and executive function have been reported in people with CHD (14), and a systematic review found that exercise-based rehabilitation consistently improved executive function in people with cardiovascular disease (21). Exercise training in people with CHD has been observed to increase regional cerebral perfusion (13), regional grey matter volume (22) and white matter integrity (23). However, changes in resting CBv and the cardiovascular and cerebrovascular autoregulatory responses to sudden perturbations (e.g. sitting-to standing response) were not altered with exercise-based cardiac rehabilitation (24).

While water-based exercise has been shown to improve body composition, aerobic capacity and strength in older populations (25-27) and in people with CHD (28, 29), the impact on cerebrovascular outcomes remains equivocal. Acute water-based exercise in 30-32°C water elevated CBv compared to matched intensity land-based exercise in healthy, young adults (2, 30, 31). Whether these effects translate to training benefits in older individuals remains uncertain. Twelve to 24 weeks of water walking in older adults did not

change resting CBv (18, 32), although in older adults with type 2 diabetes Nordic water-walking improved some cerebrovascular responses to hypercapnia, which correlated with improved aspects of cognitive function (32). Additionally, in healthy older adults, the assessment of dynamic cerebral autoregulation (dCA) revealed an improvement in very low frequency (VLF) normalised gain with water-walking, compared to land-based walking (18), indicative of improvement in dCA via more efficient dampening of the CBv response in relation to changes in systemic blood pressure (33).

Previous studies investigating water-based exercise training on cerebrovascular outcomes have used aerobic exercise training modalities (18, 32), which produce sustained elevation in CBv in response to steady-state exercise (30). A combined aerobic and resistance circuit exercise program may induce greater fluctuations in blood pressure and blood flow, particularly as circuit training involves short duration exercise bouts across a range of exercises. Exercise modality can affect peripheral blood flow responses (34, 35), so it is feasible that a varied training stimulus, combined with the impacts of water immersion, may optimise the regulation of cerebral perfusion responses in the face of blood pressure change. However, the effects of water-based mixed-modality exercise training on cerebrovascular function in patients with CHD has not been established. In this randomised controlled trial, we hypothesised that twelve weeks of water-based circuit training exercise (WEX) would enhance changes in resting CBv, neurovascular coupling (NVC) responses to a visual paradigm, and dCA in people with CHD, compared with gym-based circuit training exercise (GEX).

5.3 Methods

5.3.1 Study design

This was a randomised, control study comparing 12 weeks of WEX, GEX or control (usual activities), with assessments at baseline and 12-week follow-up. Following the provision of written, informed consent participants were allocated to the training or control groups through block randomisation, with participants selecting a sealed, opaque envelope to determine their grouping. The study was registered *a priori* with the Australian New Zealand Clinical Trials Registry (ACTRN12616000102471). The Ethical Principals from the Declaration of Helsinki were adhered to in this project and participants provided written informed consent. Ethical approval was provided by Royal Perth Hospital Human Research Ethics Committee (ref RGS0000002071), with reciprocal approval from the Human

Research Ethics Committees of Curtin University (ref: HR227/2015) and The University of Western Australia (Ref: RA/4/1/8382).

5.3.2 Participants

Adults with stable, CHD were recruited from a tertiary hospital and the local community. Inclusion criteria were; a CHD diagnosis (previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or diagnostic imaging demonstrating ≥50% occlusion of ≥1 coronary artery) on stable medication for at least 1 month. Participants were excluded if they had undergone coronary intervention or experienced a myocardial infarction in the past 6 months, or had any of the following; a diagnosis of heart failure or an ejection fraction <45%, musculoskeletal, neurological or other impairment that would prevent exercise training, including adverse responses to cardiopulmonary exercise testing (ischaemic signs or symptoms <4 METs, new onset left bundle branch block, or ventricular tachyarrhythmia), current or recent (last 6 months) history of smoking, or cancer treatment involving chemotherapy or radiotherapy. People medicated with insulin and those currently taking part in supervised exercise training, or having done so in the last 3 months, were also excluded.

5.3.3 Assessments

All participants attended the lab after fasting for at least six hours, avoiding caffeine, alcohol and moderate to vigorous physical activity or exercise for 24 hours (36). Participants were instructed to take all their usual medications at their usual times. Testing sessions were conducted at the same time of day pre- and post-intervention to exclude the effects of diurnal variation (36).

A ST3 2 MHz Transcranial Doppler (TCD) ultrasound (Spencer Technologies, Seattle, WA, USA) was used to assess CBv in the middle cerebral artery (MCA) and posterior cerebral artery (PCA). Probes were held in place with a Marc 600 headframe (Spencer Technologies, Seattle, WA). Data was exported by PowerLab (AD Instruments, Sydney, Australia) to LabChart version 8 software (ADInstruments, Sydney, Australia). Concurrent measures of beat-by-beat blood pressure were recorded by the Finapres Nova (Finapres Medical Systems, Amsterdam, The Netherlands), ECG data was recorded (BIO Amp, ADInstruments, Sydney, Australia), and end-tidal carbon dioxide was measured by a calibrated gas analyser (ML 206, ADInstruments, Sydney, Australia). Labchart files were blinded before analysis by a person external to the study.

5.3.3.1 Resting data

Participants were seated with feet resting on the floor (or a foot-rest if unable to reach the floor) for 20 minutes during instrumentation with the devices. Subsequently, resting CBv and blood pressure data were recorded for five minutes, with the best three to five minutes averaged in equal epochs, with areas of high signal noise and ectopy excluded from the analysis.

5.3.3.2 Neurovascular coupling

In participants who had an adequate PCAv signal, NVC was assessed after baseline measures. Table height and screen distance were adjusted to maintain a neutral head position and these distances were recorded. The visual stimulus was a black and white checkerboard displayed on a computer screen, inverting at a 0.5Hz interval, with a red dot centralised for participants to focus on during eyes open periods. A four-minute baseline was collected (two minutes of eyes open, followed by two minutes of eyes closed). Subsequently, five to six repetitions of 30 seconds eyes open followed by 30 seconds of eyes closed, were recorded. At least 3 trials of 30 seconds of eyes open and 30 seconds of eyes closed were used for the analysis. Trials containing significant noise or interference were excluded from analysis. Automated neurovascular software (iNVC; Innovate Calgary, Phillips, Ainslie, Chan, Lam, 2020) was used to analyse the data, with calculations detailed in Phillips *et al.* (2016) (37).

5.3.3.3 Cerebral autoregulation

The ability of the cerebrovascular system to dampen the MCAv response to changes in systemic blood pressure (dynamic cerebral autoregulation; dCA) was assessed at rest for five minutes and in response to a three-minute shallow squat-stand protocol conducted at a frequency of 0.167Hz (repeating 3 second shallow squats, followed by 3 second stands). The shallow squat protocol was found to be appropriate for measuring dCA in older individuals (38) and evidence suggests 180 seconds is able to produce valid transfer function analysis (TFA) estimates in populations where 300 seconds is not possible (39). Analysis was conducted using Ensemble-R software (Elucimed, Otago, New Zealand), which incorporates international guideline recommendations for analysis (40). Coherence, gain, normalised gain and phase data were extracted from the low frequency (LF; 0.07-0.20 Hz) and very low frequency (VLF; 0.02-0.07Hz) ranges and cases with phase wrap-around were excluded from the analysis of phase data as per current guidelines (41). Coherence

represented the relationship between blood pressure oscillation and CBv, with 0 representing no relationship and 1 representing CBv passively changing with blood pressure (33). Gain and normalised gain represent the degree of damping of the blood pressure changes in the CBv signal, with lower gain representing greater damping (i.e. better regulation) (33).

5.3.3.4 Blood pressure

Blood pressure was assessed during the resting cerebral measures, with the average taken of three automated measures (IntelliSense® Professional Digital Blood Pressure Monitor HEM-90XL, Omron Healthcare Inc., Kyoto, Japan).

5.3.4 Exercise training

Training sessions were conducted in an outpatient setting at a tertiary hospital, either in a cardiac rehabilitation gymnasium (GEX), or hydrotherapy pool (WEX) with participants submersed to their xiphoid process in 34.5°C water. Participants trained for one hour, three times per week, for 12 weeks. Circuit training was applied in both WEX and GEX groups and involved three sets of 15 exercises, with alternating aerobic and resistance stations. Each exercise in the circuit lasted for 45 seconds, followed by a 15 second active recovery. Participants commenced by performing 1 circuit, increasing to 3 circuits per session by week 3.

Exercise intensity was prescribed based on the maximal heart rate (HR_{max}) during a graded exercise test at baseline and was monitored throughout training with Polar heart rate monitors (A300, FT4 and FT7, Polar Electronics, Guangzhou, China). Aerobic stations commenced at 50-65% of HR_{max} for the first two weeks of training, progressing to 60-65% for weeks 3-4, 60-70% for weeks 5-6, 70-80% for weeks 7-8, and 80% for weeks 9-12. Participants were kept below any ischaemic threshold identified during their baseline exercise test. Borg rating of perceived exertion (RPE) (42) was monitored and progressed from 11-14 over the course of the program. WEX aerobic exercises involved walking or jogging across the pool, and high knees stepping on the spot. GEX aerobic exercises involved treadmill walking or jogging, and cycle ergometry.

Resistance exercises were matched for muscle group between interventions and involved hip flexion/extension and abduction/adduction, knee flexion/extension, shoulder abduction/adduction and elbow flexion/extension (28). The exercise circuit is described in detail in Supplementary Material 1. Resistance exercises in the GEX group were performed

utilising stack weight machines, pulley machines, dumbbells and ankle weights. Weights were increased once participants could achieve 12- 15 lifts with an RPE <13 (“hard”) and good technique. Resistance exercises in the WEX group utilised custom-designed double-sided acrylic paddles to maximise drag resistance. (Supplementary Material 1). A metronome (Tempo Trainer Pro, FINIS, Tracy, USA) guided cadence for the exercises. Exercises were progressed once RPE fell below 13 by increasing the speed of movement, or the paddle size, whilst maintaining the same range of movement.

5.3.5 Data analysis

Data were analysed with STATA 16.1 software (StataCorp LLC, Texas, USA). Generalised linear mixed models were used to examine group-time interactions and within-group changes in pre and post training data. Results were summarised using estimated marginal means, mean differences and 95% confidence intervals. Ladder of powers, based on the Tukey methodology, was used to assess normality of outcome data in order to determine appropriate transformations or canonical links. Median [interquartile ranges] of raw data are also reported. The level of significance was set at alpha=0.05.

5.4 Results

Fifty-two participants were randomised with 11 WEX, 14 GEX and 10 control participants completing at least one cerebrovascular or blood pressure outcome measure at both baseline and follow up. Baseline characteristics are described in Table 5.2. Pre-post resting data was available for MCAv in 10 WEX, 14 GEX and 9 control participants, and for PCAv in 10 WEX, 12 GEX and 8 control participants (Table 5.3). The numbers of pairs analysed are included in Table 5.3, with reasons for excluding scans from analysis reported in Supplementary Material 2; the main reasons being *a priori* inability to insonate the target vessel (n=5 MCA, n=4 PCA) and loss to follow-up (n=7 WEX, n=2 GEX, n=1 control). Additionally, one control participant's blood pressure trace was incomplete, so they were excluded from blood pressure derived resting measures.

Table 5.2 Baseline characteristics of participants who completed cerebrovascular or resting blood pressure outcome measures in the study.

Characteristic	WEX (n=11)	GEX (n=14)	Control (n=10)
Age *(yr),* Mean (SD)	64.7 (8.0)	66.2 (8.5)	71.9 (5.2)
Sex, males/females	9/2	13/1	9/1
Weight (kg), Mean (SD)	82.2 (14.3)	84.1 (12.8)	80.6 (11.0)
BMI ($kg.m^2$), Mean (SD)	28.0 (4.3)	28.4 (4.0)	27.2 (3.1)
Cardiac history, n (%)			
Asymptomatic	2 (18)	1 (7)	2 (20)
Angina (no MI)	3 (27)	5 (36)	3 (30)
MI	6 (55)	8 (57)	5 (50)
Years since Dx, Median (range)	3.0 (0.8-12)	2.4 (0.5-29)	5.0 (0.5-16)
Management, n (%)			
Coronary bypass graft	1 (9)	6 (43)	5 (50)
Stent	8 (73)	10 (71)	5 (50)
Stent and coronary bypass	0 (0)	2 (14)	1 (10)
Non-invasive treatment	2 (18)	0 (0)	1 (10)
Comorbidities, n (%)			
Cancer (excluding basal cell carcinoma)	2 (18)	4 (29)	2 (20)
Metabolic (pre/T2DM)	1 (9)	2 (14)	2 (20)
Neurologic (CVA/TIA)	0 (0)	1 (7)	2 (20)
Other cardiovascular	1 (9)	0 (0)	0 (0)
Musculoskeletal	7 (64)	5 (36)	8 (80)
Respiratory	2 (18)	2 (14)	2 (20)
Medications, n (%)			
Antiplatelet/anticoagulant	11 (100)	13 (93)	10 (100)
Lipid lowering	10 (91)	13 (93)	9 (90)
Beta blockers	3 (27)	7 (50)	8 (80)
ACE inhibitors	5 (45)	9 (64)	4 (40)
Angiotensin II receptor blockers	2 (18)	3 (21)	5 (50)
Calcium channel blockers	0 (0)	2 (14)	3 (30)
Diuretic	0 (0)	1 (7)	1 (10)
Glucose lowering	0 (0)	1 (7)	2 (20)
Proton pump inhibitors	3 (27)	2 (14)	3 (30)

WEX: water-based circuit training exercise group; GEX gym-based circuit training exercise group; n: number of participants; Dx: diagnosis; BMI: body mass index; MI: myocardial infarction; T2DM: type 2 diabetes mellitus; CVA: cerebrovascular accident; TIA: transient ischaemic attack; ACE: angiotensin converting enzyme

5.4.1 Resting outcomes

There were no changes in resting MCAv, or MCA conductance or pulsatility index (PI) in any group over the 12 weeks (Table 5.3). Mean PCAv and PCA conductance did not significantly change over time in any group. PCA PI increased over time with WEX

(+0.09AU, p=0.002) and was significantly different to the effect over time of GEX (p=0.019). For blood pressure measurements data was available from 10 control, 14 GEX and 11 WEX pairs. There were no between group differences in systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial blood pressure (MAP) from pre- to post intervention (Table 5.3).

5.4.2 Dynamic cerebral autoregulation

The control group was omitted from statistical analysis, as only 4 (rest) and 2 (squat stand) participants had data meeting criteria for coherence analysis. Wrap-around of phase data excluded analysis, per guidelines (41). No significant changes were observed in LF data at rest or during squat-stands (Table 5.4). In contrast, estimated mean change in resting VLF gain (0.26 $cm.s^{-1}.mmHg^{-1}$; CI 95%: 0.08 to 0.45 $cm.s^{-1}.mmHg^{-1}$, p = 0.005) and normalised gain (0.46 $\%.mmHg^{-1}$; CI 95%: 0.08 to 0.84$\%.mmHg^{-1}$, p= 0.018) were significantly increased following GEX. Total differences between WEX and GEX resting VLF gain differed by -0.35 $cm.s^{-1}.mmHg^{-1}$ (95% CI: -0.62 to -0.09 $cm.s^{-1}.mmHg^{-1}$, p=0.010) with a -0.57 $\%.mmHg^{-1}$ (-1.13 to -0.01 $\%.mmHg^{-1}$) change in normalised gain (Table 5.4). Additionally, whilst the reduced dCA gain in the VLF range after WEX (-0.14 $cm.s^{-1}.mmHg^{-1}$; 95% CI: -0.30 to 0.02 $cm.s^{-1}.mmHg^{-1}$, p=0.077) during squat stands was not significant, it was directionally different (p = 0.003) compared to the significant change observed in the GEX group (0.19 $cm.s^{-1}.mmHg^{-1}$; 95% CI: 0.03-0.34 $cm.s^{-1}.mmHg^{-1}$, p = 0.017). The total difference between WEX and GEX during squat-stands in VLF gain was -0.33 $cm.s^{-1}.mmHg^{-1}$ (-0.55 to -0.11 $cm.s^{-1}.mmHg^{-1}$, p=0.003), which remained different when gain was normalised to -0.51 $\%.mmHg^{-1}$ (-0.76 to - 0.26$\%.mmHg^{-1}$, p<0.001) (Table 5.4).

Table 5.3 The effects of 12 weeks of WEX, GEX or control period on resting cerebrovascular and blood pressure outcomes.

	CON				WEX					GEX					
	n	Week 0	Week12	p1	n	Week 0	Week 12	p1	p2	n	Week 0	Week 12	p1	p2	p3
SBP (mmHg)	10	122 (114-131)	118 (110-127)	0.325	11	121 (113-129)	115 (107-124)	0.125	0.730	14	116 (108-123)	114 (107-122)	0.742	0.589	0.353
DBP (mmHg)	10	73 (67-79)	72 (66-78)	0.493	11	72 (62-72)	68 (62-74)	0.056	0.410	14	67 (62-72)	66 (61-71)	0.363	0.949	0.408
MAP (mmHg)	10	89 (83-96)	87 (81-93)	0.381	11	88 (82-94)	84 (78-90)	0.068	0.533	14	83 (78-88)	82 (77-87)	0.508	0.809	0.355
MCAv ($cm.s^{-1}$)!	9	40.1 (34.5-45.7)	40.4 (34.8-46.0)	0.885	10	49.0 (43.7-54.3)	48.1 (42.8-53.4)	0.679	0.697	14	45.1 (40.6-49.6)	46.1 (41.6-50.6)	0.563	0.804	0.491
MCA PI (AU)	9	1.00 (0.90-1.11)	0.96 (0.86-1.09)	0.153	10	0.99 (0.89-1.09)	1.02 (0.92-1.11)	0.327	0.087	14	1.03 (0.94-1.11)	1.03 (0.95-1.11)	0.826	0.210	0.544
MCA CVCi ($cm.s^{-1}.mmHg^{-1}$)	8	0.41 (0.34-0.49)	0.42 (0.35-0.50)	0.663	10	0.51 (0.44-0.58)	0.50 (0.43-0.56)	0.680	0.548	14	0.49 (0.43-0.55)	0.48 (0.43-0.54)	0.772	0.601	0.898
PCAv ($cm.s^{-1}$)!#	8	28.0 (23.4-32.6)	28.6 (24-33.2)	0.771	10	34.7 (30.5-38.8)	35.9 (31.8-40.1)	0.499	0.815	12	35.5 (31.8-39.3)	35.6 (31.9-39.4)	0.951	0.852	0.647
PCA PI (AU)	8	0.97 (0.86-1.08)	1.01 (0.90-1.11)	0.237	10	0.96 (0.87-1.06)	1.05 (0.96-1.15)	**0.002**	0.237	12	1.05 (0.96-1.13)	1.04 (0.96-1.13)	0.934	0.332	**0.019**
PCA CVCi ($cm.s^{-1}.mmHg^{-1}$)	7	0.28 (0.22-0.34)	0.31 (0.25-0.37)	0.272	10	0.35 (0.30-0.41)	0.37 (0.31-0.42)	0.536	0.656	12	0.40 (0.35-0.45)	0.38 (0.33-0.43)	0.317	0.139	0.258
$P_{ET}CO_2$ (mmHg)!	6	34.5 (32.2-36.8)	34.1 (31.8-36.4)	0.740	6	38.8 (36.5-41.2)	37.5 (35.2-39.8)	0.282	0.598	9	35.7 (33.8-37.6)	36.6 (34.7-38.5)	0.350	0.397	0.154

Data are estimated mean (95% confidence interval). CON: control group, WEX: water-based circuit training exercise group, GEX: gym-based circuit training exercise group, n: number of paired samples analysed for that group and outcome, p1: p value of estimated mean change between week 0 week 12, p2: p value for estimated mean change in outcome vs estimated mean change in control group, p3: p value for estimated mean change in WEX vs estimated mean change in GEX, SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; MCA: middle cerebral artery, v: velocity, PI: pulsatility index, AU: arbitrary units, CVCi: cerebrovascular conductance index, PCA; posterior cerebral artery,!: $p<0.05$ at week 0 between WEX and control, #: $p<0.05$ at week 0 between GEX and control.

Table 5.4 Cerebral autoregulation of middle cerebral artery velocity responses at rest and with forced blood pressure oscillations before and after 12 weeks of exercise training.

		WEX					GEX				WEX minus GEX	
	n	Week 0	Week 12	Est. mean Δ	p1	n	Week 0	Week 12	Est. mean Δ	p1	Est. mean Δ	p2
Resting												
Low Frequency												
Coherence	7	0.63 [0.48-0.80]	0.70 [0.54-0.80]	0.03 (-0.10-0.15)	0.656	8	0.63 [0.54-0.77]	0.61 [0.51-0.70]	-0.03 (-0.15-0.09)	0.602	0.06 (-0.11-0.23)	0.496
Gain ($cm.s^{-1}.mmHg^{-1}$)	7	0.93 [0.39-1.01]	0.86 [0.60-1.17]	0.13 (-0.16-0.43)	0.364	7	1.00 [0.54-1.18]	0.89 [0.69-1.28]	0.06 (-0.22-0.34)	0.673	0.08 (-0.33-0.48)	0.708
nGain ($\%.mmHg^{-1}$)	7	1.32 [1.18-1.85]	1.80 [1.05-2.48]	0.32 (-0.25-0.89)	0.276	8	2.19 [1.14-2.38]	1.82 [1.35-2.58]	0.05 (-0.49-0.58)	0.863	0.27 (-0.51-1.05)	0.498
Very Low Frequency												
Coherence	7	0.62 [0.53-0.69]	0.63 [0.43-0.65]	-0.03 (-0.15-0.09)	0.618	8	0.62 [0.52-0.68]	0.54 [0.42-0.63]	-0.11 (-0.22-0.01)	0.075	0.07 (-0.09-0.24)	0.393
Gain ($cm.s^{-1}.mmHg^{-1}$)	6	0.66 [0.56-0.80]	0.57 [0.41-0.67]	-0.09 (-0.29-0.11)	0.366	7	0.56 [0.35-0.95]	0.87 [0.48-1.11]	0.26 (0.08-0.45)	**0.005**	-0.35 (-0.62--0.09)	**0.010**
nGain ($\%.mmHg^{-1}$)	6	1.04 [0.87-1.37]	0.91 [0.86-1.31]	-0.11 (-0.52-0.30)	0.612	7	1.06 [0.88-1.88]	1.57 [1.06-2.31]	0.46 (0.08-0.84)	**0.018**	-0.57 (-1.13--0.01)	**0.047**
Squat-stands 0.167Hz												
Low Frequency												
Coherence^	6	0.76 [0.50-0.85]	0.76 [0.72-0.86]	0.07 (-0.13-0.27)	0.499	8	0.77 [0.67-0.84]	0.78 [0.62-0.84]	-0.01 (-0.18-0.17)	0.930	0.08 (-0.19-0.35)	0.569
Gain ($cm.s^{-1}.mmHg^{-1}$)	6	0.58 [0.53-0.75]	0.59 [0.51-0.76]	0.00 (-0.19-0.20)	0.989	8	0.40 [0.40-0.66]	0.55 [0.43-0.72]	0.06 (-0.11-0.23)	0.493	-0.06 (-0.32-0.20)	0.661
nGain ($\%.mmHg^{-1}$)	6	0.95 [0.59-1.13]	0.95 [0.87-1.22]	0.04 (-0.29-0.38)	0.798	8	0.80 [0.67-1.12]	1.07 [0.86-1.20]	0.21 (-0.08-0.50)	0.149	-0.17 (-0.61-0.27)	0.453
Very Low Frequency												
Coherence	6	0.54 [0.45-0.65]	0.57 [0.54-0.59]	0.04 (-0.06-0.14)	0.454	8	0.46 [0.38-0.59]	0.52 [0.37-0.72]	0.06 (-0.04-0.15)	0.235	-0.02 (-0.15-0.12)	0.832
Gain ($cm.s^{-1}.mmHg^{-1}$)!	5	0.61 [0.54-0.77]	0.52 [0.51-0.62]	-0.14 (-0.30-0.02)	0.077	5	0.37 [0.33-0.39]	0.46 [0.45-0.63]	0.19 (0.03-0.34)	**0.017**	-0.33 (-0.55--0.11)	**0.003**
nGain ($\%.mmHg^{-1}$)!	5	0.97 [0.77-1.00]	0.96 [0.93-0.96]	-0.04 (-0.22-0.13)	0.626	5	0.66 [0.63-0.79]	1.05 [1.02-1.23]	0.47 (0.28-0.64)	**<0.001**	-0.51 (-0.76--0.26)	**<0.001**

Week 0 and Week 12 are median [25^{th}-75^{th} percentile], Estimated mean change (95% CI) from modelled data. WEX: water-based circuit training exercise group, GEX: gym-based circuit training exercise group, p1: p value of estimated mean change between week 0 week 12, p2: p value of estimated mean change between WEX and GEX, WEX minus GEX: estimated mean change in WEX minus estimated mean change in GEX over 12 weeks, n: number of paired samples analysed, ^ data transformed for analysis, ! $p<0.05$ at week 0 between WEX and GEX.

Table 5.5 Neurovascular coupling responses.

	WEX				GEX				WEX minus GEX	
	Week 0 n=7	Week 12 n=7	Est. mean Δ	p1	Week 0 n=8	Week 12 n=8	Est. mean Δ	p1	Est. mean Δ	p2
Eyes closed baseline										
PCA V_{mean} ($cm.s^{-1}$)	31.8 (28.1-35.6)	33.4 (29.7-37.2)	1.6 (-1.1-4.2)	0.240	28.0 (24.5-31.5)	27.3 (23.8-30.8)	-0.7 (-3.2-1.8)	0.573	2.3 (-1.3-5.9)	0.214
MAP (mmHg)	103 (96-110)	98 (91-105)	-5 (-13-3)	0.263	95 (88-102)	96 (89-103)	1 (-6-9)	0.758	-6 (-17-5)	0.304
PCA PI (AU)	0.98 (0.86-1.11)	1.04 (0.91-1.16)	0.06 (-0.01-0.12)	0.097	1.09 (0.97-1.21)	1.10 (0.99-1.22)	0.01 (-0.05-0.07)	0.686	0.04 (-0.05-0.13)	0.350
PCA PR	1.65 (1.45-1.86)	1.68 (1.47-1.88)	0.02 (-0.15-0.20)	0.798	1.86 (1.67-2.06)	1.74 (1.56-1.93)	-0.12 (-0.28-0.04)	0.142	0.14 (-0.09-0.38)	0.234
PCA CrCP (mmHg)	39 (31-47)	39 (31-47)	0 (-9-8)	0.951	41 (34-48)	39 (32-47)	-2 (-10-6)	0.653	2 (-10-13)	0.793
PCA RAP $(mmHg.cm.s^{-1})^{-1}$	2.05 (1.73-2.37)	1.81 (1.49-2.13)	-0.24 (-0.58-0.10)	0.160	1.94 (1.64-2.24)	2.11 (1.81-2.41)	0.17 (-0.15-0.49)	0.297	-0.41 (-0.88-0.05)	0.082
Peak NVC response										
PCA V_{mean} ($cm.s^{-1}$)	37.6 (32.7-42.5)	39.1 (34.2-44.0)	1.5 (-1.4-4.5)	0.318	34.1 (29.5-38.7)	32.6 (28.0-37.2)	-1.5 (-4.2-1.3)	0.296	3.0 (-1.1-7.0)	0.149
Change PCA V_{mean} (%)	17.5 (12.1-23.0)	16.7 (11.3-22.1)	-0.9 (-7.0-5.3)	0.782	22.4 (17.3-27.5)	19.9 (14.9-25.0)	-2.4 (-8.2-3.3)	0.404	1.6 (-6.8-10.0)	0.714
PCA V_{max} ($cm.s^{-1}$)	60.4 (53.5-67.4)	64.0 (57.1-71.0)	3.6 (-1.3-8.5)	0.150	56.9 (50.4-63.4)	55.3 (48.8-61.8)	-1.7 (-6.2-2.9)	0.478	5.3 (-1.5-12.0)	0.125
Change PCA V_{max} (%)	15.9 (11.5-20.4)	14.2 (9.8-18.7)	-1.7 (-6.5-3.1)	0.487	18.0 (13.8-22.2)	16.9 (12.8-21.1)	-1.1 (-5.6-3.4)	0.639	-0.6 (-7.2-5.9)	0.852
MAP (mmHg)	105 (97-112)	101 (93-108)	-4 (-12-5)	0.365	98 (91-105)	99 (92-107)	1 (7-9)	0.761	-5 (-17-6)	0.384
Change MAP (%)	1.9 (0.2-3.5)	2.6 (0.9-4.2)	0.7 (-1.2-2.6)	0.467	3.1 (1.6-4.7)	3.3 (1.8-4.9)	0.2 (-1.5-2.0)	0.814	0.5 (-2.1-3.0)	0.712
PCA PI (AU)	1.10 (0.96-1.24)	1.14 (1.00-1.28)	0.04 (-0.03-0.12)	0.263	1.16 (1.02-1.30)	1.18 (1.04-1.32)	0.02 (-0.05-0.09)	0.622	0.03 (-0.08-0.13)	0.630
PCA PR	1.77 (1.54-2.00)	1.76 (1.53-1.98)	-0.02 (-0.25-0.22)	0.900	1.98 (1.77-2.19)	1.81 (1.60-2.03)	-0.17 (-0.39-0.05)	0.133	0.15 (-0.17-0.48)	0.351
PCA CrCP (mmHg)	42 (34-50)	41 (33-49)	-1 (-11-8)	0.808	44 (37-51)	41 (34-49)	-3 (-12-6)	0.526	2 (-11-14)	0.798

PCA RAP ($mmHg.cm.s^{-1})^{-1}$	2.15 (1.81-2.49)	1.96 (1.62-2.30)	-0.19 (-0.50-0.11)	0.216	2.03 (1.72-2.35)	2.17 (1.85-2.48)	0.13 (-0.15-0.42)	0.360	-0.33 (-0.75-0.09)	0.126
Time to peak PCA V_{max} (s)	9.5 (4.8-14.1)	11.4 (6.7-16.0)	1.9 (-4.0-7.7)	0.527	16.4 (12.0-20.7)	12.8 (8.4-17.1)	-3.6 (-9.1-1.9)	0.197	5.5 (-2.5-13.5)	0.179
PCA V_{mean} ($cm.s^{-1}$) averages										
Baseline 5 sec	31.5 (27.5-35.5)	32.8 (28.8-36.7)	1.3 (-1.1-3.6)	0.294	28.0 (24.3-31.7)	27.3 (23.6-31.0)	-0.6 (-2.9-1.6)	0.565	1.9 (-1.3-5.1)	0.246
0-5sec	33.3 (29.0-37.6)	35.1 (30.8-39.4)	1.8 (-0.8-4.4)	0.175	29.8 (25.8-33.8)	29.0 (25.0-33.1)	-0.8 (-3.2-1.6)	0.523	2.6 (-1.0-6.1)	0.154
5-10sec	35.7 (31.0-40.4)	38.0 (33.3-42.7)	2.3 (-0.6-5.2)	0.120	31.8 (27.4-36.2)	30.4 (26.0-34.8)	-1.4 (-4.1-1.3)	0.309	3.7 (-0.3-7.7)	0.067
10-15sec	36.2 (31.3-41.2)	38.8 (33.8-43.7)	2.5 (-0.6-5.7)	0.119	32.3 (27.7-36.9)	31.0 (26.4-35.6)	-1.3 (-4.2-1.7)	0.405	3.8 (-0.6-8.1)	0.088
15-20sec	35.3 (30.5-40.1)	38.1 (33.3-42.8)	2.8 (-0.3-5.8)	0.073	31.6 (27.1-36.0)	31.2 (26.8-35.7)	-0.3 (-3.2-2.5)	0.826	3.1 (-1.1-7.3)	0.144
20-25sec	34.7 (30.2-39.3)	36.0 (31.5-40.5)	1.3 (-1.3-3.8)	0.328	31.1 (26.9-35.4)	30.1 (25.9-34.4)	-1.0 (-3.4-1.4)	0.404	-2.3 (-1.2-5.7)	0.199
25-30sec	33.3 (28.8-37.8)	35.1 (30.6-39.6)	1.8 (-1.0-4.6)	0.214	31.6 (27.3-35.8)	30.4 (26.1-34.6)	-1.2 (-3.8-1.4)	0.375	3.0 (-0.9-6.9)	0.130

Data are estimated mean (95% confidence interval). WEX: water-based circuit training exercise group, GEX: gym-based circuit training exercise group, n: number of samples in analysis, p1: p value of estimated mean change between week 0 week 12, p2: p value of estimated mean change between WEX and GEX, WEX minus GEX: estimated mean change in WEX minus estimated mean change in GEX over 12 weeks, PCA: posterior cerebral artery, V_{mean}: mean velocity, V_{max}: maximum velocity, MAP: mean arterial pressure, PI: pulsatility index, AU: arbitrary units, PR: pulse ratio, CrCP: critical closing pressure, RAP: resistance area product.

5.4.3 Neurovascular coupling

Four GEX and 3 WEX participants were excluded due to signal noise. Control participants were not included in the statistical analysis, as only 4 participants who had PCA measures had data with adequate quality for analysis due to ectopy or noise. In the baseline to peak response analysis there were no significant differences between groups (Table 5.5). When PCAv mean response was averaged in 5 second segments, the change in WEX was not significantly different from GEX for any interval, although the 5 to 10 second (3.7 $cm.s^{-1}$, p=0.067) and 10 to 15 second (3.8 $cm.s^{-1}$, p=0.088) responses tended to increase more with WEX (Table 5.5).

5.5 Discussion

This study is the first to compare the effects of water and land-based exercise training on cerebral autoregulation in people with stable CHD. We observed directionally different adaptations in the VLF spectrum for gain and normalised gain between WEX and GEX responses. These differences suggest that water-based exercise may represent a unique and beneficial physiological stimulus for improving cerebrovascular perfusion-pressure regulation. Whilst the differential effect of WEX compared to GEX on PCAv mean response during NVC (p=0.067) and DBP (p=0.056) did not reach statistical significance, these preliminary findings support further research into the effects of water-based exercise on cerebrovascular health.

Cardiometabolic conditions can impair dCA (43, 44), a marker of the capacity of the brain to buffer changes in blood pressure to maintain perfusion (33). We found reduced VLF gain and normalised gain in WEX, compared to GEX, over 12 weeks. This observation is consistent with previous findings of reduced VLF normalised gain (from induced blood pressure oscillations) in response to 24 weeks of water walking, compared to land walking, in healthy older adults (18). The gain derived from the transfer function analysis represents the degree of dampening in the MCAv signal, compared to the change in blood pressure, with lower gain representing more effective regulation (33). This may indicate an improved ability for the brain to maintain perfusion during perturbations, such as postural changes (33).

The effects of hydrostatic pressure, superimposed on exercise, may underpin the differences in the cerebrovascular stimulus between water- and land-based exercise

modalities, explaining the dCA findings we observed. During immersion, hydrostatic pressure acts on the lower body, driving increased venous return, preload and cardiac output (5-7). Accordingly, CBv has been found to exhibit greater increases during water-immersed exercise than land-based exercise at a matched-intensity during 30-32°C water immersion (2, 30, 31), indicating that the cerebrovasculature likely had different CBv exposures during this study.

While the clinical implications of the effect of WEX on dCA remain to be fully elucidated, the MCAv and MAP response to a rapid stand challenge was blunted in people with CHD compared to controls (24), indicating autoregulation may be impaired. In people with CHD, six months of land-based exercise training did not change the rapid stand challenge MAP or MCAv responses (24), suggesting other modalities of exercise may be required to elicit improvements in dCA (18). While dCA directly relates to cerebrovasculature capacity to buffer changes in systemic blood pressure and cope with positional changes (33), impaired dCA has been associated with other adverse clinical states. In adults with hypertension and/or diabetes, increased LF gain was associated with lower fractional anisotropy (reduced white matter integrity) (45). This suggests an association between impairment in cerebral autoregulation and the risk of developing adverse changes to white matter. Furthermore, increased LF normalised gain has been associated with orthostatic hypotension and dementia in people with Parkinson's disease (46), indicating there may be links between cerebrovascular function and cognitive and autonomic pathology.

Further research is required into how these changes would impact people with CHD who have risk factors for developing orthostatic intolerance, such as older age (47), and the use of diuretic, nitrate and beta blocker medications (48). The beneficial effect of WEX compared to GEX on dCA in our study is meaningful, considering the population studied has a higher risk of orthostatic intolerance. Coupled with the increased aerobic capacity and improvement in body composition in this (28) and previous water immersion studies (25, 26), WEX as a physical health modality should be considered for future research into optimising exercise training and improving cerebrovascular function in this population.

Despite divergent responses in dCA between groups, no changes in resting MCAv or PCAv were observed in this study. This is consistent with findings from our group in healthy older adults following 24 weeks of water or land-based walking exercise (18), and with data from older adults with type 2 diabetes who performed Nordic walking in the pool 3 times per week for 12 weeks (32). In a similar population to this study, Coombs *et al.* (2023) examined the effects of 6 months of land-based cardiac rehabilitation exercise in people

with CHD and found no change in resting MCAv over time (24). It seems likely that resting cerebrovascular functional measures are preserved by redundant compensatory mechanisms in humans.

In the current study MCA PI was unchanged, while PCA PI increased (0.09AU, p=0.002) in the WEX group over the 12-week intervention, although not to a greater extent than the control group. PI is an indicator of small vessel cerebral resistance, with an increase in PI considered to reflect an increase in small vessel tone (37), although haemodynamic factors other than cerebrovascular resistance have been noted to impact PI (49). While previous research has found an association between elevated MCA PI and mild cognitive impairment in people with hypertension (50), the clinical effects of elevated PCA PI have not been determined. In the present study the change in PCA PI from week 0 to week 12 was of a similar magnitude to the differences seen with the NVC stimulus that occurs in seconds (PCA PI change at week 0 was +0.07AU with GEX and +0.12 AU with WEX), and remained within the range of normal values of 0.5-1.19AU (51), suggesting that it is unlikely that this finding is associated with negative clinical implications.

The peak PCAv NVC response was not altered by exercise training and the change in mean PCAv during the eyes open response phase from baseline to week 12 in WEX compared to GEX between 5-10 and 10-15 seconds did not reach statistical significance (3.7 $cm.s^{-1}$, p=0.067 and 3.8 $cm.s^{-1}$, p=0.088, respectively). The lack of significant change in NVC response following exercise training in this study is similar to findings in healthy older adults (18). The 24 week land or water walking intervention in healthy adults ≥50 years utilised a similar visual paradigm to assess NVC as the present study and did not find any training related changes in PCAv responses (18). In healthy aging, PCAv mean responses to NVC are reduced compared to younger adults (52) and disease states such as hypertension can impair the function of cerebral vessels and NVC responses (53), which may contribute to the lack of significant change seen in the present study.

While the effect on blood pressure did not reach significance between groups in the present study, the 4mmHg reductions in DBP and MAP (p=0.056 and p=0.068 respectively) in the WEX cohort should encourage further research in this area. A 24 week study in people with heart failure by Caminiti *et al*. (2011) found combined water and land based exercise significantly reduced DBP (-11mmHg) compared to land-based exercise alone (-4mmHg), however the baseline DBP measures were greater than in the current study (87-88mmHg compared to 67-73mmHg) (54). In populations with hypertension, water-based training has been found to be effective for reducing SBP and DBP (55), and was at least as effective as

land-based exercise in doing so (56), suggesting WEX may be more effective for reducing blood pressure in people with hypertension.

Water-based exercise interventions have been found to have a range of health benefits for older adults and clinical populations. This WEX program was also found to improve endothelial function (57), aerobic capacity, leg strength and body fat (28) in people with CHD. Studies in older adults and people with diabetes have seen positive changes in lean mass (26), body fat percentage (32), endothelial function (58), aerobic capacity (25), functional strength (32) and glycaemic control (32), in addition to the cerebrovascular benefits of improved dCA (18), reduced MCA pulsatility index (32), and increased cerebrovascular conductance in response to hypercapnia (32). Furthermore, improvement in cognition has been seen with Nordic water-walking in people with type 2 diabetes and this was correlated with changes in cerebrovascular function (32). Taken together, these studies support larger future studies into the effects of water-based exercise training on cerebrovascular and cognitive function in people with CHD, and people at risk of cardiovascular disease or cognitive decline.

5.5.1 Limitations

Transcranial Doppler assessment of CBv is extensively used in the literature, with benefits including high temporal resolution, being non-invasive, non-radioactive, allowing for dynamic and low risk assessments. A potential limitation of this methodology is the reliance upon the assumption of constant target vessel diameter (59), both during the assessment session, and over the exercise program or control period, however, MCA diameter was found to be acutely stable in the absence of high levels of hypercapnia (60). A further limitation of this study is the relatively small sample size, resulting from several factors including participant attrition, signal interference, particularly from ectopy or irregular rhythms, poor tolerance of the positions and equipment by participants, musculoskeletal comorbidities, and difficulty insonating some participants, highlighting the challenges inherent in a RCT of this nature. Nonetheless, interventional training studies are important and robust approaches, as cross-sectional comparisons of trained vs untrained subjects are diluted by self-selection bias and myriad between-subject factors that impact human physiology. Future studies focusing on cerebrovascular outcomes of participants with cardiovascular disease may need to undertake screening tests prior to study enrolment to minimise the impact of these threats to internal validity. In healthy older adults approximately 11% of those assessed in a 24 week water-walking study were unable to be insonated,

highlighting this is not a problem unique to this study (18). Furthermore, these effects may be compounded in a population with CHD, given the observed reductions in MCAv (24) and increased risk of arterial tortuosity (61), which may limit the ability to insonate at an appropriate angle. Future studies may consider the addition of methods such as magnetic resonance imaging, which may counter some of the technical challenges of the current study, however the ability to do functional tests, such as repeated squats, would be limited.

This study excluded patients within 6 months of a cardiac event or intervention, with heart failure, and those medicated with insulin, limiting the generalisability of the findings to these cohorts. Additionally, participants were tested whilst taking usual medications, such as beta blockers and ACE-inhibitors, which may alter haemodynamic responses (62), and endothelial function. However, we determined it would be unethical to ask participants to cease any medications. Moreover, maintaining usual medications makes the results readily transferable to the clinical setting. In the context of these limitations, our preliminary findings should encourage further research into the effects of WEX on cerebrovascular function across diverse cohorts of people with CVD and an expanded set of outcome measures.

5.6 Conclusions

This exploratory study in people with CHD found changes in dynamic cerebral autoregulation between WEX and GEX, suggesting that water based mixed-modality exercise performed in the upright posture may be more beneficial for the brain's ability to buffer blood pressure changes. Further research is needed to determine the longer-term effects of this stimulus on orthostatic tolerance, cerebrovascular health and cognition in people with CHD. While the effect of exercise training on NVC outcomes didn't reach significance in the current study, future studies involving larger sample sizes and a broader range of neurovascular outcomes are warranted to more conclusively evaluate the potential clinical utility of WEX, an emerging exercise modality for people with cardiovascular disease.

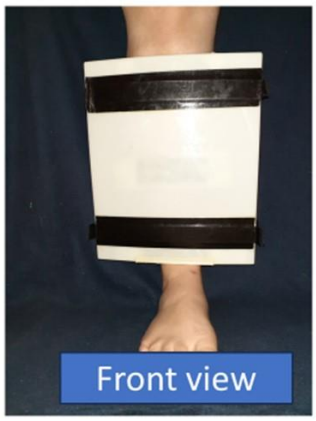
5.7 Supplementary Material

5.7.1 Supplementary material 1

Supplementary Material 1. Exercise Training Programs

Exercises for water (WEX) and gym (GEX) exercise training programs. Each circuit consisted of 15 exercises; 3 circuits completed per session (after 3 weeks). As WEX is only concentric exercise, some exercises were split to ensure even muscle activity over the course of the program. This was achieved by alternating 2 circuit layouts- 'A' and 'B' and starting with the opposite circuit each training session – e.g. session 1 would be A,B,A, session 2 would be B,A,B. Exercises marked 'all' were completed each circuit, those marked 'A' were in circuit A only, those marked 'B' were in circuit B only.

Exercise	GEX Circuit	WEX Circuit
1	Treadmill walk/jog (all)	High knees (all)
2	Bilateral knee extension (all)	Right knee flexion/ extension (all)
3	Cycle ergometer (all)	Walking or jogging (all)
4	Bilateral hamstrings (all)	Left knee flexion/ extension (all)
5	Treadmill walk/ jog (all)	High knees (all)
6	Shoulder adduction (A) Shoulder abduction (B)	Bilateral shoulder abd/add'n (all)
7	Cycle ergometer (all)	Walking or jogging (all)
8	Right hip flexion (A) Right hip extension (B)	Right hip flexion/ extension (all)
9	Treadmill walk/ jog (all)	High knees (all)
10	Left hip flexion (A) Left hip extension (B)	Left hip flexion/ extension (all)
11	Cycle ergometer (all)	Walking or jogging (all)
12	Bilateral elbow flexion (A) Bilateral elbow extension (B)	Elbow flexion/ extension (all)
13	Treadmill walk/ jog (all)	High knees (all)
14	Right hip abduction (A) Left hip abduction (B)	Right hip abduction (A) Left hip abduction (B)
15	Cycle ergometer (all)	Walking or jogging (all)



Resistance paddle design
Depicting placement for leg flexion/extension exercises.
For leg abduction/ adduction the paddle is rotated 90 degrees on the leg.

Figure 5.1 Supplementary material 1 exercise training programs.

5.7.2 Supplementary material 2

Analysis limitations:

Resting and overall session data limitations:

The main data limitation was being unable to insonate MCA in 3 WEX, 1 GEX, 1 control participants, and PCA in 1 WEX, 2 GEX, 1 control participants. Insonation was performed by a trained PhD student and checked by an experienced cerebrovascular researcher (Author K.S.). Other limitations included an inability to attend the follow up CBv session within the 1 week post-training window due to illness or travel (2 WEX, 1 control participants). Furthermore, near syncope (inability to tolerate the testing session) occurred in 2 GEX participants and signal noise affected readings from 1 GEX and 1 control participants for some measures.

Dynamic cerebral autoregulation:

Resting analysis was conducted in 7 WEX and 8 GEX participants. This was due to inadequate signal or signal interruption in 3 WEX participants, and 4 GEX participants and blood pressure trace interference in 2 GEX participants. The squat-stand analysis was conducted in 6 WEX and 8 GEX participants, due to musculoskeletal pain in 1 WEX participant, signal noise or failure in 2 WEX and 3 GEX participants, and ectopy affecting signals in 1 WEX and 3 GEX participants. The transfer function analysis software determined there was inadequate coherence for reliable gain and normalised gain measures in the VLF band for 1 WEX participant at rest, and 1 WEX and 3 GEX participants during squat stands. The control group was omitted from statistical analysis, as only 4 (resting) and 2 (squat stand) control participants had data suitable for coherence analysis. Wrap-around of phase data should be excluded from analysis (per current guidelines) leaving insufficient data for phase analysis.

5.8 References

1. Carter HH, Spence AL, Pugh CJ, Ainslie P, Naylor LH, Green DJ. Cardiovascular responses to water immersion in humans: impact on cerebral perfusion. Am J Physiol Regul Integr Comp Physiol. 2014;306:R636-R40.
2. Carter HH, Pienaar O, Coleman A, Cheng JL, MacDonald MJ, Naylor LH, et al. The effects of water temperature on cerebral blood flow during aquatic exercise. Eur J Appl Physiol. 2024;124:219-5.
3. Bressel E, Louder TJ, Raikes AC, Alphonsa S, Kyvelidou A. Water immersion affects episodic memory and postural control in healthy older adults. J Geriatr Phys Ther. 2019;42(4):E1-E6.
4. Mano T, Iwase S, Saito M, Koga I, Abe H, Inamura K, et al. Neural and humoral controlling mechanisms of cardiovascular functions in man under weightlessness simulated by water immersion. Acta Astronaut. 1991;23:31-3.
5. Gauer O. Recent advances in the physiology of whole body immersion. Acta Astronaut. 1975;2:31-9.
6. Gabrielsen A, Warberg J, Christensen N, Bie P, Stadeager C, Pump B, et al. Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am J Physiol Regul Integr Comp Physiol. 2000;278:1583-8.
7. Christie J, Sheldahl L, Tristani F, Wann L, Sagar K, Levandoski S, et al. Cardiovascular regulation during head- out water immersion exercise. J Appl Physiol. 1990;69:657-64.
8. Sato D, Onishi H, Yamashiro K, Iwabe T, Shimoyama Y, Maruyama A. Water immersion to the femur level affects cerebral cortical activity in humans: Functional near-infrared spectroscopy study. Brain Topogr. 2012;25(2):220-7.
9. Hashitomi T, Hoshi D, Fukuie M, Tarumi T, Sugawara J, Watanabe K. Differences in the prefrontal cortex responses of healthy young men performing either water-based or land-based exercise at light to moderate intensity. Exp Brain Res. 2023;241(4):991-1000.
10. Schaefer SY, Louder TJ, Foster S, Bressel E. Effect of water immersion on dual-task performance: Implications for aquatic therapy. Physiother Res Int. 2016;21(3):147-54.
11. Bressel E, Vakula MN, Kim Y, Bolton DAE, Dakin CJ. Comparison of motor skill learning, grip strength and memory recall on land and in chest-deep water. PLoS One. 2018;13(8):e0202284.
12. Moraca R, Lin E, Holmes Iv JH, Fordyce D, Campbell W, Ditkoff M, et al. Impaired baseline regional cerebral perfusion in patients referred for coronary artery bypass. J Thorac Cardiovasc Surg. 2006;131(3):540-6.
13. Anazodo UC, Shoemaker JK, Suskin N, Ssali T, Wang DJJ, St. Lawrence KS. Impaired cerebrovascular function in coronary artery disease patients and recovery following cardiac rehabilitation. Front Aging Neurosci. 2016;7(224).
14. Gayda M, Gremeaux V, Bherer L, Juneau M, Drigny J, Dupuy O, et al. Cognitive function in patients with stable coronary heart disease: Related cerebrovascular and cardiovascular responses. PLoS One. 2017;12(9):e0183791.
15. Alosco ML, Gunstad J, Jerskey BA, Xu X, Clark US, Hassenstab J, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. Brain Behav. 2013;3(6):626-36.

16. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLoS One. 2017;12(9):e0184244-e.
17. Ovsenik A, Podbregar M, Fabjan A. Cerebral blood flow impairment and cognitive decline in heart failure. Brain Behav. 2021;11(6):e02176.
18. Green D, Kurt. S, Maslen B, Cox K, Lautenshlager N, Pestell C, et al. The impact of six-month land versus water walking on cerebrovascular function in the aging brain. Med Sci Sports Exerc. 2021 53(10):2093-100.
19. Bliss ES, Wong RHX, Howe PRC, Mills DE. The effects of aerobic exercise training on cerebrovascular and cognitive function in sedentary, obese, older adults. Front Aging Neurosci. 2022;14:892343.
20. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for alzheimer disease: A randomized trial. JAMA. 2008;300(9):1027-37.
21. Dabbaghipour N, Javaherian M, Moghadam BA. Effects of cardiac rehabilitation on cognitive impairments in patients with cardiovascular diseases: a systematic review. Int J Neurosci. 2021;131(11):1124-32.
22. Anazodo UC, Shoemaker JK, Suskin N, St.Lawrence KS. An investigation of changes in regional gray mattter volume in cardiovascular disease patients, pre and post cardiovascular rehabilitation. Neuroimage Clin. 2013;3:388-95.
23. Poirier SE, Suskin NG, Khaw AV, Thiessen JD, Shoemaker JK, Anazodo UC. Probing evidence of cerebral white matter microstructural disruptions in ischemic heart disease before and following cardiac rehabilitation: A diffusion tensor MR imaging study. J Magn Reson Imaging. 2023;Epub ahead of print.
24. Coombs GB, Al-Khazraji BK, Suskin N, Shoemaker JK. Impact of ischemic heart disease and cardiac rehabilitation on cerebrovascular compliance. J Appl Physiol (1985). 2023;135(4):753-62.
25. Haynes A, Naylor LH, Carter HH, Spence AL, Robey E, Cox KL, et al. Land-walking vs. water-walking interventions in older adults: Effects on aerobic fitness. J Sport Health Sci. 2020;9(3):274-82.
26. Naylor LH, Maslen BA, Cox KL, Spence AL, Robey E, Haynes A, et al. Land- versus water-walking interventions in older adults: Effects on body composition. J Sci Med Sport. 2020;23(2):164-70.
27. Bento PCB, Rodacki ALF. Muscle function in aged women in response to a water-based exercises program and progressive resistance training. Geriatr Gerontol Int. 2015;15(11):1193-200.
28. Scheer A, Shah A, Ito Ramos de Oliveira B, Moreno-Suarez I, Jacques A, Green D, et al. Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial. J Physiother. 2021;67(4):284-90.
29. Tokmakidis SP, Spassis AT, Volaklis KA. Training, detraining and retraining effects after a water-based exercise program in patients with coronary artery disease. Cardiology. 2008;111(4):257-64.
30. Pugh CJ, Sprung VS, Ono K, Spence AL, Thijssen DHJ, Carter HH, et al. The effect of water immersion during exercise on cerebral blood flow. Med Sci Sports Exerc. 2015;47(2):299-306.
31. Parfitt R, Hensman MY, Lucas SJE. Cerebral blood flow responses to aquatic treadmill exercise. Med Sci Sports Exerc. 2017;49(7):1305-12.
32. Ploydang T, Khovidhunkit W, Tanaka H, Suksom D. Nordic walking in water on cerebrovascular reactivity and cognitive function in elderly patients with type 2 diabetes. Med Sci Sports Exerc. 2023;55(10):1803-11.

33. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559.
34. Thijssen DHJ, Dawson EA, Black MA, Hopman MTE, Cable NT, Green DJ. Brachial artery blood flow responses to different modalities of lower limb exercise. Med Sci Sports Exerc. 2009;41(5):1072-9.
35. Green DJ, Bilsborough W, Naylor LH, Reed C, Wright J, O'Driscoll G, et al. Comparison of forearm blood flow responses to incremental handgrip and cycle ergometer exercise: relative contribution of nitric oxide. J Physiol. 2005;562(Pt 2):617-28.
36. Thijssen DHJ, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol. 2011;300(1):H2-12.
37. Phillips AA, Chan FH, Zheng MMZ, Krassioukov AV, Ainslie Philip N. Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. J Cereb Blood Flow Metab. 2016;36(4):647-64.
38. Batterham AP, Panerai RB, Robinson TG, Haunton VJ. Does depth of squat-stand maneuver affect estimates of dynamic cerebral autoregulation? Physiol Rep. 2020;8(16):e14549.
39. Burma JS, Miutz LN, Newel KT, Labrecque L, Drapeau A, Brassard P, et al. What recording duration is required to provide physiologically valid and reliable dynamic cerebral autoregulation transfer functional analysis estimates? Physiol Meas. 2021;42(4):44002.
40. Claassen JAHR, Meel-van den Abeelen ASS, Simpson DM, Panerai RB. Transfer function analysis of dynamic cerebral autoregulation: A white paper from the International Cerebral Autoregulation Research Network. J Cereb Blood Flow Metab. 2016;36(4):665-80.
41. Panerai RB, Brassard P, Burma JS, Castro P, Claassen JAHR, van Lieshout JJ, et al. Transfer function analysis of dynamic cerebral autoregulation: a CARNet white paper 2022 update. J Cereb Blood Flow Metab. 2023;43(1):3-25.
42. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81.
43. Junejo RT, Braz ID, Lucas SJE, van Lieshout JJ, Phillips AA, Lip GYH, et al. Neurovascular coupling and cerebral autoregulation in atrial fibrillation. J Cereb Blood Flow Metab. 2019;40(8):1647-57.
44. Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. Am J Physiol Heart Circ Physiol. 2015;308(7):H681-H7.
45. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2014;34(2):228-34.
46. Chen H, Xu E, Zhou F, Li Q, Zeng J, Mei S, et al. Impaired dynamic cerebral autoregulation: A potential mechanism of orthostatic hypotension and dementia in Parkinson's disease. Front Aging Neurosci. 2022;14:927009.
47. Finucane C, O'Connell MDL, Fan CW, Savva GM, Soraghan CJ, Nolan H, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study. Circulation. 2014;130(20):1780-9.
48. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A. Drug-related orthostatic hypotension: Beyond anti-hypertensive medications. Drugs Aging. 2020;37(10):725-38.

49. de Riva N, Budohoski KP, Smielewski P, Kasprowicz M, Zweifel C, Steiner LA, et al. Transcranial doppler pulsatility index: What it is and what it isn't. Neurocrit Care. 2012;17(1):58-66.
50. Harris S, Reyhan T, Ramli Y, Prihartono J, Kurniawan M. Middle cerebral artery pulsatility index as predictor of cognitive impairment in hypertensive patients. Front Neurol. 2018;9(538).
51. Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial doppler ultrasound: A review of the physical principles and major applications in critical care. Int J Vasc Med. 2013;2013:629378.
52. Nowak-Flück D, Ainslie PN, Bain AR, Ahmed A, Wildfong KW, Morris LE, et al. Effect of healthy aging on cerebral blood flow, CO2 reactivity, and neurovascular coupling during exercise. J Appl Physiol. 2018;125(6):1917-30.
53. Girouard H, Iadecola C. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. J Appl Physiol. 2006;100(1):328-35.
54. Caminiti G, Volterrani M, Marazzi G, Cerrito A, Massaro R, Sposato B, et al. Hydrotherapy added to endurance training versus endurance training alone in elderly patients with chronic heart failure: a randomized pilot study. Int J Cardiol. 2011;148:199-203.
55. Guimaraes GV, de Barros Cruz LG, Fernandes-Silva MM, Dorea EL, Bocchi EA. Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: A randomized controlled trial (HEx trial). Int J Cardiol. 2014;172(2):434-41.
56. Arca EA, Martinelli B, Martin LC, Waisberg CB, Franco RJdS. Aquatic exercise is as effective as dry land training to blood pressure reduction in postmenopausal hypertensive women. Physiother Res Int. 2014;19(2):93-8 6p.
57. Scheer AS, Ito Ramos De Oliveira B, Shah A, Jacques A, Chasland LC, Green DJ, et al. The effects of water-based circuit exercise training on vascular function in people with coronary heart disease. Am J Physiol Heart Circ Physiol. 2023;325(6):H1386-H93.
58. Haynes A, Naylor LH, Spence AL, Robey E, Cox KL, Maslen BA, et al. Effects of land- vs water-walking interventions on vascular function in older adults. Med Sci Sports Exerc. 2021;53(1):83-9.
59. Ainslie PN, Hoiland RL. Transcranial Doppler ultrasound: Valid, invalid, or both? J Appl Physiol. 2014;117(10):1081-3.
60. Verbree J, Bronzwaer A-SGT, Ghariq E, Versluis MJ, Daemen MJAP, van Buchem MA, et al. Assessment of middle cerebral artery diameter during hypocapnia and hypercapnia in humans using ultra-high-field MRI. J Appl Physiol. 2014;117(10):1084-9.
61. Ciurică S, Lopez-Sublet M, Loeys BL, Radhouani I, Natarajan N, Vikkula M, et al. Arterial tortuosity. Hypertension. 2019;73(5):951-60.
62. Priel E, Wahab M, Mondal T, Freitag A, O'Byrne PM, Killian KJ, et al. The Impact of beta blockade on the cardio-respiratory system and symptoms during exercise. Curr Res Physiol. 2021;4:235-42.

Chapter 6. Discussion

6.1 Overview

This thesis reports the first randomised, controlled trial investigating a WEX program for people with stable coronary heart disease (CHD). The findings from this study support WEX being an appropriate form of exercise to GEX for people with stable CHD. In agreeance with the first hypothesis, Chapter 3 highlighted WEX increased VO_{2peak} to a similar extent as GEX. In addressing the second hypothesis, that WEX and GEX would similarly impact the secondary outcome measures of muscular strength, body composition, blood profiles and blood pressure, Chapter 3 found both WEX and GEX increased lower limb strength and reduced body fat, while Chapter 4 observed an improvement in triglycerides with GEX, and Chapter 5 demonstrated a tendency for blood pressure outcomes to improve with WEX. These findings highlight both exercise modalities were able to improve secondary outcome measures. Finally, in addressing the third hypothesis, that WEX would provide benefits to endothelial and cerebrovascular function, Chapter 4 found WEX provided benefits to endothelial function, not evident with GEX performed at a similar relative intensity and involving similar muscle groups, and Chapter 5 observed that WEX may induce more favourable cerebral autoregulatory responses compared to GEX. These findings highlight that WEX is an appropriate alternative exercise modality for people with CHD which may be of specific benefit for improving vascular and cerebrovascular dysfunction.

6.2 Addressing potential barriers to exercise in people with coronary heart disease

Engaging people with CHD in regular, ongoing exercise is an important for the secondary prevention of further cardiovascular events, and is associated with improvements in fitness, cardiovascular risk factors, and cardiovascular mortality (1, 2). A meta-analysis of studies involving people with CHD who maintained an active lifestyle over the long term (study follow up periods ranging from 4.2-15.7 years), compared to people who remained inactive, reported that both all-cause and cardiovascular mortality were lowered by approximately 50% in the active cohorts (3). Furthermore, improvements in, or higher levels of, aerobic capacity, endothelial function and leg strength (outcomes which were improved with WEX in the present project) have been shown to be associated with improved survival in people with CHD (4-7).

While the benefits of exercise are well established for people with CHD, attendance rates at cardiac rehabilitation are often sub-optimal and physical activity levels are often below recommended guidelines (8-12). There are many potential reasons for this, including work pressures (13, 14), transportation or logistic issues (13-15), motivation and personal preferences (14, 16), and the impact of physical issues or comorbidities (13, 15, 17, 18).

The physical properties of water immersion may provide a solution to some of these barriers. Musculoskeletal pain or discomfort has been associated with reduced exercise participation in people with CHD (17, 18). Water-immersion reduces the weight bearing load in proportion to the amount of the body submerged, and can also modulate pain (19), which potentially may help to alleviate some of the discomfort experienced by some people during exercise (20). Indeed, in patients with heart failure who undertook water-based exercise there was moderate agreement (7/10 on a Likert scale) that exercising in the water reduced their self-rated musculoskeletal pain (21), and 76% of people with CHD who undertook land and water-based maximum exercise tests found the water-based test more comfortable (22). Ensuring patients are comfortable during exercise is important to optimise exercise adherence, as unpleasant experiences during exercise can reduce exercise participation (23). For example, reasons identified for people dropping out of exercise-based cardiac rehabilitation have included a fear of provocation of musculoskeletal conditions, or pain or discomfort with exercise (13), with 15% of withdrawals from cardiac rehabilitation in women and 9% in men being related to musculoskeletal issues (14). In addition to being a key component of secondary prevention (24), exercise is important for arthritis management (25). Recent exercise guidelines for people with osteoarthritis noted similar efficacy between water- and land-based exercise and suggest water-based exercise may be beneficial for those unable to exercise on land due to it being too difficult to perform, or too pain provocative (26). Given that a high proportion (up to 60%) of people with CHD experience some degree of comorbid arthritis (18), the inclusion of WEX as a suitable exercise modality for patients with CHD may help to increase exercise participation in this population.

Water-based exercise may also address additional barriers to exercise for sub-populations of people with CHD. Fear of falling has been associated with reduced exercise participation in people with CHD (27) and a meta-analysis concluded that in adults with CHD aged 50 years and over, there was an adjusted odds ratio of 1.13 (95% CI 1.05-1.23) for falls (28). In people hospitalised for a myocardial infarction, approximately 10% and 36% were classified as high and moderate falls risk, respectively (29). The hazard ratio for death within 12 months was 3.65 (95% CI 1.67-7.99) for those classified as high falls risk,

compared to those classed as a low falls risk (29). Meta-analyses have found that exercise training has a positive impact on fear of falling and falls risk factors in older adults (30), with water-based exercise and land-based exercise demonstrating similar benefits for dynamic balance (31). As a facilitator for encouraging exercise, the physical properties of water, such as buoyancy and viscosity, assist in supporting the body and would slow the body down in the event of a fall (19), reducing the chance of injury. These factors may encourage exercise training in the large cohort of people with CHD who are at risk of falling.

Aside from physical comorbidities, motivation is an important component of exercise adherence in people with CHD (16). A literature review in people with chronic disease identified the importance of finding enjoyment in an exercise program to enhance adherence to the regimen (23). A key concept related to this is that what is enjoyable (or unpleasant) to one person may be different to that of a different person (23), emphasising the importance of having a broad range of exercise modalities supported by evidence for this patient group to cater to individual preferences.

Exercise modalities that are effective for improving function and reducing risk factors are an integral component of cardiac rehabilitation and the secondary prevention of further adverse cardiovascular events, or complications (32). Local and international guidelines for exercise prescription in cardiac rehabilitation highlight the importance of applying a patient centred approach, which relies on individualised options for exercise prescription (32-34) . The findings from this thesis support the prescription of water-based exercise as a safe and effective exercise training modality that increases the range of effective exercise options available, facilitating patient choice, along with assisting in reducing barriers to exercise across a variety of subgroups of people with CHD.

6.3 The efficacy of water-based circuit exercise training in people with coronary heart disease

The literature on upright, water-based exercise training in people with CHD can be broadly categorised into two types of exercise programs- short-term intensive inpatient rehabilitation programs (35-39) and longer duration outpatient or community programs (40-43). To date, the water-based exercise programs investigated in people with CHD have included aerobic (43), aerobic with some added resistance (42), a water-based gymnastic/callisthenic component of a combined program (35, 36, 39), or both aerobic and resistance training, conducted over separate sessions (37, 38, 40, 41). The studies undertaken and presented in this thesis are the first to describe the effects of a water-based

circuit training program, involving alternating bouts of aerobic and resistance exercises performed during each training session. A summary of the impact of the WEX intervention as described in this thesis, on aerobic capacity, muscular strength, body composition, vascular function, cerebrovascular function and cardiovascular risk factors, is presented below.

6.3.1 Aerobic capacity

The present project was the first to examine the impact of water-based aerobic and resistance circuit training on peak oxygen uptake (VO_{2peak}), the gold standard measure of aerobic capacity, in people with CHD (44). As outlined in Chapter 3, WEX significantly increased VO_{2peak} over the 12 week duration of the program compared to the control group, with no significant differences seen between WEX and GEX, supporting the first hypothesis. The magnitude of change over time was +1.8ml.kg^{-1}.min^{-1} and +2.5ml.kg^{-1}.min^{-1} compared to the control group. This improvement is comparable to that seen in a large (n=1,171) trial of 36 land-based exercise session in a phase II rehabilitation program (+1.9 ±3.3ml.kg^{-1}.min^{-1}) (4). Furthermore, in people with CHD higher VO_{2peak} is associated with improved survival (45), and an improvement of 1 ml.kg^{-1}.min^{-1} in VO_{2peak} was found to be associated with a 10% reduction in mortality (4), highlighting the clinical relevance of the improvements seen in the present project.

In relation to other water-based exercise studies in people with CHD, the effects observed in the current project were consistent with most of the previous studies (36, 39, 40, 43). The only study whose results were discordant with our findings was the short-term study by Vasić et al. (2019), who found a greater increase in VO_{2peak} with water- than land-based training (land: +2.0 ml^{-1}.kg^{-1}.min; water: +4.0 ml^{-1}.kg^{-1}.min) (37).

Interpreting the present findings in the context of previous studies, upright water-based exercise programs consistently improve aerobic capacity, measured in terms of VO_{2peak}, in a clinically meaningful way in people with CHD. Whether this occurs to a greater extent with short duration (2-3 week) high-frequency (twice daily) water-based exercise interventions, compared to land-based exercise interventions, remains unclear and warrants further research. Only two studies have compared the effects of land and water-based exercise training on VO_{2peak} in an outpatient setting, the present project, and an aerobic walking intervention (43), which observed a similar effect on aerobic capacity. Collectively, this research indicates WEX, and other forms of upright, water-based exercise are

appropriate alternatives to traditional gym-based exercise programs for improving aerobic capacity in people with CHD.

6.3.2 Muscular strength

As outlined in Chapter 3, WEX increased hamstring curl strength by 10% (significant compared to control), but while leg press strength increased over time (7%) there was not a significant effect compared to the control group. While not significantly different to the change with WEX, the GEX group increased hamstrings and leg press strength by 13% and 14% respectively (significant compared to control). This increase in leg strength with both WEX and GEX supports the second hypothesis, that both modalities would improve muscular strength. Limited changes were seen in upper limb strength, however, divergent from our second hypothesis, GEX significantly increased biceps strength compared to WEX, and latissimus dorsi pulldown strength compared to control. In the present project some participants were unable to complete 1 repetition maximum testing due to musculoskeletal limitations (7,3,4 and 10 participants for leg press, hamstring curl, bicep curl and latissimus dorsi pulldown, respectively), which may have impacted the results. Given the high prevalence of musculoskeletal comorbidities in this population, the inclusion of submaximal or functional measures of strength may be worth considering for future research projects, and in clinical practice.

Only limited studies have investigated the impact of water-based training on muscular strength in people with CHD. Tokmakidis et al. (2008) found that whole body strength increased 12% over four months, with an increase seen in both upper and whole-body strength summated measures (40). Compared to the present project, Tokmakidis et al. included four dedicated exercises involving the upper body (40), compared to two in the present project, which may explain the difference seen between studies. Another study that measured strength by Volaklis et al. (2007) only provided a measure of whole-body strength, reporting 12% and 13% increases with water- and land-based training, respectively (41), suggesting comparable effects between water and land-based training. Findings from other populations involving people with type 2 diabetes (46) and healthy older females (47) have failed to find significant improvement in pectoral deck strength and latissimus dorsi pulldowns respectively, although improvements in chest press strength were seen in healthy older females (47).

In people with CHD, increased quadriceps strength has been found to be associated with improved survival (6), and in older adults, increased lower limb muscle strength has

been correlated with improved functional and gait outcomes (48, 49), highlighting the importance of the lower-limb strength increases observed in the present study. Further research into whether WEX interventions can be refined for improving upper limb strength is required. There are several exercise options that could be investigated to this end, including body weight resistance on the pool wall, buoyancy or elastic resisted exercises, or supplementary hand weight exercises.

6.3.3 Body composition

Chapter 3 presented anthropometric and dual energy x-ray absorptiometry (DXA) results, the first study to do so when investigated the effectiveness of WEX in people with CHD. While there were no significant differences between groups for anthropometric data, further detail from the DXA scans revealed 1.1kg (95% CI -2.3 to 0.0kg) and 1.2kg (-2.3 to -0.1kg). reductions in mean fat mass compared to the control group for WEX and GEX, respectively, in support of the second hypothesis that WEX and GEX would similarly improve body composition. Excessive fat mass is associated with a pro-inflammatory state and can contribute to atherogenesis (50). Correspondingly, high body fat percentage has been associated with increased risk of major adverse coronary events in people with CHD (51).

Other water-based exercise training programs in people with CHD have found reductions in adiposity assessed using the sum of skinfolds (40, 41) and bioimpedance analysis (43), though this finding was not universal (42). In studies in people with CHD comparing water to land-based exercise, measures of adiposity were found to reduce to a similar extent (41, 43). Thus, our finding supports this literature that WEX reduces body fat to a similar degree to GEX (51).

Accompanying the reduction in adiposity, increased lean mass index is associated with a reduced risk of major cardiovascular adverse events in people with CHD (51). The present study found a small reduction in lean mass with WEX compared to GEX (-0.7kg, 95% CI -1.4 to -0.1kg), although the individual group differences were 0.4kg or less, which is within the acknowledged margin of accuracy for lean tissue for the DXA machine used (0.61-0.86kg) (52-54).

6.3.4 Vascular function

As outlined in Chapter 4, WEX improved FMD percentage change, a measure of vascular endothelial function, from 4.0% (95% CI 3.0 to 5.1%) to 5.3%, (95% CI 4.1 to 6.5%),

while it remained stable with GEX. While the increase in FMD with WEX supports the third hypothesis, that WEX would improve endothelial function, the difference between WEX and GEX was not significant. Endothelial dysfunction underpins atherosclerosis, the underlying pathology in CHD (55-57). A meta-analysis found prognostic value in FMD assessment in people with CVD, with a 16% reduction in the risk of adverse cardiovascular events per 1% higher FMD score (58). In people with stable CHD, diagnosed at least 6 months previously, a singular FMD assessment was found to be useful for predicting adverse events (59). Furthermore, in people admitted for angiography with a new CHD diagnosis, lasting impairment in FMD over six months was associated with an increased risk of adverse cardiovascular events, independent of an improvement in traditional risk factors (5). These studies highlight the importance of improving endothelial function in people with CHD.

Land-based exercise training has been found to improve coronary (60) and peripheral artery endothelial function (61) in people with CHD. This is considered to be driven by the recurrent exposure to transient increases in shear stress on arterial walls that occurs with exercise training (62). The physical properties of water immersion may augment the shear stress stimulus induced during exercise, resulting from a complex interplay of hydrostatic pressure and thermal effects (63). While the current project demonstrated an improvement in FMD with WEX, the mechanism of this change was not elucidated, and it may reflect a combination of influences; exercise-induced shear stress, hydrostatic pressure and thermal effects.

Few studies have examined the impact of water-based training on endothelial function in people with CHD, with the current project being the first study outside of a high frequency, inpatient rehabilitation program to examine this outcome. Consistent with findings in the current thesis, short-duration inpatient water-based exercise programs have been found to improve markers of endothelial function (36, 37). In people recovering from a recent coronary event or intervention, two weeks of high-frequency, inpatient, water or land based exercise training increased FMD (37), while a 3 week high-frequency, inpatient study of land alone, or land and water-based exercise, found increases in metabolites of nitric oxide (associated with endothelial function) with the land and water group, but not the land alone group (36). The difference in FMD findings for GEX in the present project, compared to the two-week study, may be due to the influence of a different shear stress pattern provoked by the training stimulus (continuous aerobic exercise or gym sessions compared to alternating exercises), or the acuity of the patients. Data from these intensive studies support the findings of WEX improving FMD, and together with the results of the present

project, suggest similar benefits to endothelial function are available to people with CHD from a less-intensive exercise regimen that would be more suited to maintaining ongoing exercise.

6.3.5 Cerebrovascular function

The impact of water-based exercise training on cerebrovascular function in people with CHD has not previously been reported in the literature. The exploratory study in the present thesis, reported in Chapter 5, supported the third hypothesis that WEX would improve cerebrovascular function, with the observation that WEX had reduced gain and normalised gain in the low frequency spectrum during dynamic cerebral autoregulation assessment compared to GEX. These changes are indicative of improved dynamic cerebral autoregulation (the ability of the cerebrovasculature to counteract changes in systemic blood pressure (64)), supporting future research into the impact of WEX on cerebrovascular function in people with CHD.

People with CHD have been observed to have changes in the grey (65, 66) and white (67) matter structures of the brain, reductions in regional cerebral perfusion (68), resting middle cerebral artery velocity (69) and are at increased risk of developing cognitive impairment or dementia (70). Functionally, cardiometabolic conditions can lead to impairments in dynamic cerebral autoregulation (71, 72), which is an indicator of how well the brain can buffer changes in blood pressure (64). Additionally, cerebral perfusion responses to stimuli can be blunted with ageing and hypertension (73, 74), suggesting that people with CHD are at risk of functional cerebrovascular changes.

In people with CHD, exercise training has been found to ameliorate some of the deleterious adaptations seen in the grey (65) and white matter (67), perfusion changes (68) and aspects of cognitive function (75), although the optimum exercise prescription for improving cerebrovascular health has not been determined.

In healthy older adults, 24 weeks of water walking demonstrated some benefit over land-walking for improving dynamic cerebral autoregulation, through exhibiting improvement in very low frequency normalised gain (76), with the present study supporting this finding. A recent study investigating the effects of land-based exercise training on the cerebral autoregulatory response to a rapid stand test in people with CHD and found no difference in mean arterial pressure or MCAv responses after exercise training (69), suggesting alternate training modalities should be considered if an improvement in cerebrovascular function is a

desired outcome. The adverse cerebral and cognitive changes observed in people with CHD highlight the systemic nature of the disease, and the need for exercise strategies to be developed that target improvements in brain health, with this project supporting the inclusion of water-based exercise modalities in future research.

6.3.6 Other outcome measures

Other markers that have been associated with cardiovascular risk that were assessed in the studies presented in this thesis include blood profile markers, reported in Chapter 4, and resting blood pressure, outlined in Chapter 5.

In the current study, blood profiles remained relatively stable across the 12-week period. The only significant change in the lipid profile measures occurred in triglycerides in the GEX group, with a 17% reduction over time ($p=0.022$) and a trend for a reduction compared to control ($p=0.059$), but not WEX ($p=0.232$). While higher levels of triglycerides have been associated with increased risk of atherosclerotic events in people with CHD (77), low density lipoprotein cholesterol (LDL-C) has been acknowledged as the leading atherogenic lipoprotein in recent lipid management guidelines, and is the primary target of medical management (78-80). Neither HDL-C or LDL-C were found to be significantly altered in the present project, consistent with previous studies comparing land and water-based exercise in people with CHD (41, 43). A study of aerobic, resistance and combined land-based exercise training in people with CHD found total cholesterol and LDL-C took eight months to improve (81). This suggests a longer duration training program may be needed to induce changes in other assays of the lipid profile.

As discussed in Chapter 4, fibrinogen was significantly reduced with GEX compared to WEX and control, although the 5% reduction did not reach significance within the GEX group over the 12 weeks. Fibrinogen has been associated with increased mortality risk in people with CHD with a J-shaped association (lowest mortality between 2.95 and 3.69 $g.L^{-1}$) (82). Both training groups in the present study remained within the optimal zone throughout the study period, although the control group increased to just outside the upper margin at the end of the 12-week period. The present project found no changes in other blood markers associated with adverse outcomes in people with CHD, such as C-reactive protein (83) or renal function (estimated glomerular filtration rate (84)) in any group.

Chapter 5 outlined changes in blood pressure in a sub-group of the study sample who completed cerebrovascular outcome measures. While there were no differences

between groups, there was a tendency for WEX to reduce DBP by ~6% over the 12 weeks (p=0.056). Other studies of WEX have observed similar findings (36, 43). Conversely, in people with resistant hypertension, water-based exercise training was found to reduce SBP and DBP (85). Collectively, it appears the degree of change in blood pressure with water-based exercise training in people with, or at risk of, CHD may depend on the degree of hypertension at baseline.

In summary, GEX, may favourably influence triglycerides and fibrinogen levels, and WEX may benefit DBP. An observation of note was the relatively sound control of lipid profile, fibrinogen and blood pressure compared to other studies, which may help to explain the lack of changes observed in the present study. Larger trials with greater variability in risk factors may provide further evidence for the efficacy of WEX and GEX in improving these measures.

6.4 Limitations

The participants included in this study were all stable and had lived with a CHD diagnosis for at least 6 months prior to study entry. While this means the program is readily translatable to the large population of people living with CHD as a chronic condition, caution should be applied to extending the results to the acute and sub-acute phase of cardiac rehabilitation. Intensive rehabilitation programs conducted early following a cardiac event (< four weeks) that had water-based exercise components (not circuit training specifically) were well tolerated and effective (36, 37), suggesting the exercise program prescribed in the current project may be suitable as the exercise component in a Phase II cardiac rehabilitation program taking place within 6 months of a coronary event, though further research is required.

People with CHD and comorbid CHF were not included in this study in order to maintain a relatively homogenous cohort, so the findings cannot be extended to patients with CHF. Historically, there have been concerns regarding the suitability of water-based exercise for patients with CHF, due to the potential for increasing pulmonary artery/capillary wedge pressures and left ventricular overload (86). However, several studies have reported findings of improved ventricular function during water immersion (87, 88) and that water-based training was well tolerated and effective for maintaining or improving functional fitness outcomes for people with CHF (36, 89-91). To date, there have not been any studies which have examined the effects of water-based circuit training involving alternating aerobic and resistance exercise in CHF, presenting a valuable opportunity for future research.

Patients with other severe comorbid conditions that limit exercise, such as severe musculoskeletal or respiratory conditions, were excluded from the present project to allow the exercise program to be standardised. A study sample that includes patients with an extensive range of comorbidities should be included in future research to ensure the program can be developed to suit as broad a range of individuals as possible. Given the merits of water-based exercise for people with arthritis, this is an especially important group to target. While the participants were on stable medications prior to study entry, one GEX participant reduced their dose of a beta blocker during the study and one WEX participant increased their cholesterol lowering medication in the final week of training. The GEX participant did not contribute MCAv data, and the WEX participant did not produce paired dynamic cerebral autoregulation measures, as such they did not impact the analysis of dynamic cerebral autoregulation. Their removal from FMD analysis did not impact the significance of the within-group FMD% results and there was no change to the significance of total cholesterol in the WEX group when the WEX participant with the medication change was removed. The impact of other medications could impact certain outcome measures, indeed, our results cannot be extrapolated to participants taking insulin, as insulin can acutely impact vascular endothelial function assessments, and so was an exclusion for this trial (92).

There were also study limitations associated with the sample size for strength testing, due to musculoskeletal pain in some participants. The inclusion of submaximal or functional measures of strength (e.g. 30 second chair sit to stand test) are worthy of consideration for inclusion in future research to monitor those limited by pain on maximal testing. Furthermore, for vascular function and aerobic capacity outcomes, the present sample size may not be adequately powered to detect small, between-group changes.

As outlined in Chapter 5, the investigation of cerebrovascular function poses some interesting questions for future research into optimising exercise for enhancing cerebrovascular function in people with CHD. The change in dCA response indicates the need for future research into the effects of WEX on cerebral blood flow in people with CHD. We suggest pre-screening participants for future studies in this area to ensure potential participants have an adequate window for the assessment of the target vessels with ultrasound and to assess their ability to tolerate the outcome measures. Furthermore, the presence of arrhythmias and ectopic beats, which are common in people with CHD, reduced the number of measures within an outcome that could be assessed in some instances, so increasing the number of trials per outcome would be advisable.

6.5 Directions for future research

While the results presented in this thesis suggest water-based exercise is an appropriate modality for people with CHD, there are several avenues for future research that could be applied to help develop this modality for uptake in clinical practice. While positive changes to endothelial function were observed with WEX, establishing the physiological basis for the vascular changes seen requires further investigation. Additionally, further examination of the cognitive and cerebrovascular effects of WEX are warranted from the promising exploratory findings of this thesis. Finally, further research into translating water-based exercise into routine clinical practice is needed, and this should be underpinned by research involving health economics and implementation science approaches.

6.5.1 Establishing the physiological mechanisms of vascular changes with water-based exercise

Differentiating the thermal and hydrostatic effects and their contributions to peripheral and cerebrovascular responses to water-based exercise in people with CHD may help to further optimise training regimens for people with CVD. A randomised controlled trial of exercising in different water-temperatures could be used to determine the mechanism of benefit from WEX and to inform how best to tailor water-based exercise for optimal outcomes in clinical practice.

6.5.1.1 Acute responses to acute water- based exercise in people with coronary heart disease

While some research has been conducted in healthy individuals into the acute effects of water immersion and water-based exercise on cerebrovascular (93-95), peripheral vascular (63, 96), and sympathetic nervous system responses (97, 98), the effects in people with CHD are unknown.

Researching the acute effects of water-based exercise in people with CHD is important, as responses may differ from young, healthy controls due to the well-established impairments in endothelial function that are present in people with CHD (99), and attenuated cerebrovascular exercise responses in people with cardiometabolic conditions (100-102). Additionally, sympathetic activation can mediate vascular responses to exercise (103), and while activation is reduced during water immersion in healthy people (97, 98), this attenuation is blunted with age (104) and people with CHD demonstrate elevated sympathetic nervous system activation (105).

Questions to consider for acute water-based exercise studies in people with CHD:

- What are the acute effects of water immersion and water-based exercise on peripheral limb and cerebrovascular blood velocity / shear / arterial diameter in people with CHD?
- What are the impacts on sympathetic nervous system function, peripheral vascular resistance and cardiac outcomes at rest and during exercise?
- How do these effects vary with different water temperatures and depth?
- What are the impacts of low and moderate intensity drag resisted exercises on peripheral and cerebral blood flow velocities and thermoregulation during immersion?

Answering these questions will help inform the optimal water temperature, depth and exercises for translation into clinical practice.

6.5.1.2 Isolating the effects of water-based exercise training and repeated water immersion

In the present study, participants in the WEX group were exposed to an exercise training stimulus and water immersion. Both have the potential to increase shear stress, a known mediator of endothelial function (62, 106). Within the water immersion stimulus there are both thermal (skin heating (98, 107)) and hydrostatic effects (central volume shift, with increased limb blood flow (98, 108)) that can create increases in shear stress. Future studies are required that isolate the immersion stimulus from the exercise training stimulus. This could be examined through using a repeated immersion group as a comparator to water-based exercise training. If thermoneutral immersion alone is beneficial to vascular health this may prove to be a treatment option for patients with severely impaired mobility, or deconditioning.

Another consideration for future research would be investigating the effects of training in different water temperatures. For example, determining whether outcomes differ after training in a hydrotherapy pool (typically 34-35°C) compared with a community heated pool (typically 28-30°C). This would help to guide which pool type and temperature is required for optimising vascular benefits in people with CHD.

6.5.2 Examining the broader cognitive and cerebrovascular responses to water-based exercise training in people with coronary heart disease

Given the structural and perfusion changes in the brain with CHD (65, 67, 68), and the link between CHD and cognitive dysfunction (70), interventions to improve cerebrovascular health in this population are imperative. The exploratory work presented in Chapter 5 regarding the impact of WEX on cerebrovascular function suggests that further research into the effects of WEX on cognition and cerebrovascular function in people with and without CHD is warranted.

Given the increase in peripheral arterial FMD reported in Chapter 4, and the potential manipulation of shear stress with water-based exercise (63), examining the impact on cerebrovascular shear-mediated dilation (a recently developed assessment of the response in cerebral blood flow to a transient increase in carbon dioxide), which is known to be at least partially NO mediated (109), would provide valuable information on the impact of shear stress changes on cerebrovascular function. Furthermore, the trend for improvement in PCAv responses during neurovascular coupling assessment (reported in Chapter 5) suggests further investigation into the impact of WEX on neurovascular coupling responses is also warranted, particularly given the link between NO and peak PCAv response to a visual paradigm (110). Investigating the standard chequerboard sequence alongside a more complex visual task may be considered to provoke a greater PCAv response (111).

The use of other imaging modalities, such as magnetic resonance imaging should also be considered in future studies. Recent evidence has suggested middle cerebral artery diameter may change with exercise training over time in young hypertensive people (112). Furthermore, in people with CHD, previous studies have shown that exercise training elicited changes in grey matter volume (65) and the fractional anisotropy of white matter tracts (67), indicating magnetic resonance imaging may provide greater detail about cerebral changes and assist with interpreting changes in cerebral blood velocity measured by ultrasound. Recently combined MRI and ultrasound data have been used with computational fluid dynamic modelling to develop a detailed understanding of the impact of changing cerebral blood flow in response to various stimuli (113). Applying this technology to people with CHD may aid in identifying areas at risk in the cerebral circulation and allow for any changes in these regions with exercise training to be characterised. Studies with larger samples and running for longer durations should consider cognitive assessment batteries to ascertain if WEX is effective for improving cognitive function.

6.5.3 Determining how to translate this program into clinical practice

For WEX to be more broadly applied in clinical practice, its impact in people with comorbidities excluded from the present study need to be determined. Furthermore, if the program was to be widely adopted as a modality for outpatient cardiac rehabilitation in Australia, where many such programs are government funded, then feasibility and cost-effectiveness studies are required to support implementation. Many cardiac rehabilitation programs do not have access to a hydrotherapy pool, however we have successfully conducted a similar program in a community pool for people with type 2 diabetes (46) and future research could determine any requirements to implement this as a community-based program. Research encouraging transitioning the WEX program from supervised training to independent practise should also be considered, to assist in the maintenance of ongoing exercise participation.

6.6 Conclusion

The research presented in this thesis represents the first study to examine the effects of water-based circuit training exercise in people with stable CHD. The WEX program was well tolerated and provided similar benefits to aerobic capacity, body fat and hamstring strength as GEX. Furthermore, brachial artery endothelial function increased with WEX, and favourable changes were observed during dynamic cerebral autoregulation assessment with WEX, in comparison to GEX. These findings support WEX as a well-tolerated option for exercise prescription in people with CHD, which may have additional benefits to vascular health.

The development of effective exercise modalities that reduce barriers to exercise are important for increasing physical activity levels across the population of people with CHD. The recognition of WEX as an evidence-based mode of exercise training may help improve exercise participation rates by increasing the variety of exercise training options and by addressing barriers to exercise, such as musculoskeletal pain, by providing a low weight-bearing load option for exercise training.

6.7 References

1. Vasankari V, Halonen J, Vasankari T, Anttila V, Airaksinen J, Sievänen H, et al. Physical activity and sedentary behaviour in secondary prevention of coronary artery disease: A review. Am J Prev Cardiol. 2021;5:100146.
2. Lavie C, Milani R. Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. Prog Cardiovasc Dis. 2011;53:397-403.
3. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, et al. Systematic review of physical activity trajectories and mortality in patients with coronary artery disease. J Am Coll Cardiol. 2022;79(17):1690-700.
4. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, et al. Cardiac rehabilitation fitness changes and subsequent survival. Eur Heart J Qual Care Clin Outcomes. 2018;4(3):173-9.
5. Kitta Y, Obata J-e, Nakamura T, Hirano M, Kodama Y, Fujioka D, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol. 2009;53(4):323-30.
6. Kamiya K, Masuda T, Tanaka S, Hamazaki N, Matsue Y, Mezzani A, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. Am J Med. 2015;128(11):1212-9.
7. Barons MJ, Turner S, Parsons N, Griffiths F, Bethell H, Weich S, et al. Fitness predicts long-term survival after a cardiovascular event: a prospective cohort study. BMJ Open. 2015;5(10):e007772.
8. Norekvål TM, Bale M, Bedane HK, Hole T, Ingul CB, Munkhaugen J. Cardiac rehabilitation participation within 6 months of discharge in 37 136 myocardial infarction survivors: a nationwide registry study. Eur J Prev Cardiol. 2023:zwad350.
9. Huang W-T, Liu C-Y, Hung H-F, Hsu S-P, Chiou A-F. Gender differences in factors associated with physical activity in patients with coronary artery disease. J Cardiovasc Nurs. 2022;37(4):386-77.
10. Alsaleh E, Baniyasin F. Prevalence of physical activity levels and perceived benefits of and barriers to physical activity among Jordanian patients with coronary heart disease: A cross-sectional study. Front Public Health. 2022;10:1041428.
11. Astley CM, Chew DP, Keech W, Nicholls S, Beltrame J, Horsfall M, et al. The impact of cardiac rehabilitation and secondary prevention programs on 12-month clinical outcomes: A linked data analysis. Heart Lung Circ. 2020;29(3):475-82.
12. Briffa T, Maiorana A, Sheerin N, Stubbs A, Oldenburg B, Sammel N, et al. Physical activity for people with cardiovascular disease: recommendations from the National Heart Foundation of Australia. Med J Aust. 2006;184(2):71-5.
13. Ravn MB, Uhd M, Svendsen ML, Ørtenblad L, Maribo T. Why do patients with ischaemic heart disease drop out from cardiac rehabilitation in primary health settings. A qualitative audit of patient charts. Front Rehabil Sci. 2022;3:837174.
14. Marzolini S, Brooks D, Oh PI. Sex differences in completion of a 12-month cardiac rehabilitation programme: an analysis of 5922 women and men. Eur J Cardiovasc Prev Rehabil. 2008;15(6):698-703.
15. Resurrección DM, Moreno-Peral P, Gómez-Herranz M, Rubio-Valera M, Pastor L, Caldas de Almeida JM, et al. Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. Eur J Cardiovasc Nurs. 2019;18(1):38-47.
16. Slovinec D'Angelo ME, Pelletier LG, Reid RD, Huta V. The roles of self-efficacy and motivation in the prediction of short- and long-term adherence to exercise among patients with coronary heart disease. Health Psychol. 2014;33(11):1344-53.
17. Rocha JA, Allison TG, Santoalha JM, Araujo V, Pereira FP, Maciel MJ. Muscoloskeletal complaints in cardiac rehabilitation: prevalence and impact on cardiovascular risk factor profile and functional and psychosocial status. Rev Port Cardiol. 2015;34(2):117-23.
18. Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with heart disease--United States, 2005 and 2007. MMWR Morb Mortal Wkly Rep. 2009;58(7):165-9.
19. Becker B. Aquatic therapy: Scientific foundations and clinical rehabilitation applications Am J Phys Med Rehabil. 2009;1(9):859-72.

20. Psycharakis SG, Coleman SGS, Linton L, Kaliarntas K, Valentin S. Muscle activity during aquatic and land exercises in people with and without low back pain. Phys Ther. 2019;99(3):297-310.
21. Adsett JA, Morris NR, Kuys SS, Paratz JD, Mudge AM. Motivators and barriers for participation in aquatic and land-based exercise training programs for people with stable heart failure: A mixed methods approach. Heart Lung. 2019;48(4):287-93.
22. Choi HJ, Kim RB, Joo JS, Han YE, Kim YS, Kim MS, et al. Comparison of cardiorespiratory responses during aquatic and land treadmill exercise in patients with coronary artery disease. J Cardiopulm Rehabil Prev. 2015;35(2):140-6.
23. Collado-Mateo D, Lavín-Pérez AM, Peñacoba C, Del Coso J, Leyton-Román M, Luque-Casado A, et al. Key factors associated with adherence to physical exercise in patients with chronic diseases and older adults: An umbrella review. Int J Environ Res Public Health. 2021;18(4):2023.
24. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. J Am Coll Cardiol. 2023;82(9):833-955.
25. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020;72(2):220-33.
26. Hinman RS, Hall M, Comensoli S, Bennell KL. Exercise & Sports Science Australia (ESSA) updated Position Statement on exercise and physical activity for people with hip/knee osteoarthritis. J Sci Med Sport. 2023;26(1):37-45.
27. LaPier TK, Cleary K, Kidd J. Exercise self-efficacy, habitual physical activity, and fear of falling in patients with coronary heart disease. Cardiopulm Phys Ther J. 2009;20(4):5-11.
28. Bourke R, Doody P, Pérez S, Moloney D, Lipsitz LA, Kenny RA. Cardiovascular disorders and falls among older adults: A systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2024;79(2):1-15.
29. Manemann SM, Chamberlain AM, Boyd CM, Miller DM, Poe KL, Cheville A, et al. Fall risk and outcomes among patients hospitalized with cardiovascular disease in the community. Circ Cardiovasc Qual Outcomes. 2018;11(8):e004199.
30. Papalia GF, Papalia R, Diaz Balzani LA, Torre G, Zampogna B, Vasta S, et al. The effects of physical exercise on balance and prevention of falls in older people: A systematic review and meta-analysis. J Clin Med. 2020;9(8):2595.
31. Kim Y, Vakula MN, Waller B, Bressel E. A systematic review and meta-analysis comparing the effect of aquatic and land exercise on dynamic balance in older adults. BMC Geriatrics. 2020;20(1):302.
32. Woodruffe S, Neubeck L, Clark RA, Gray K, Ferry C, Finan J, et al. Australian Cardiovascular Health and Rehabilitation Association (ACRA) core components of cardiovascular disease secondary prevention and cardiac rehabilitation 2014. Heart Lung Circ. 2015;24(5):430-41.
33. Verdicchio C, Freene N, Hollings M, Maiorana A, Briffa T, Gallagher R, et al. A clinical guide for assessment and prescription of exercise and physical activity in cardiac rehabilitation. A CSANZ Position Statement. Heart Lung Circ. 2023; 32(9):1035-1048.
34. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021;29(1):230-45.
35. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Exercise rehabilitation restores physiological cardiovascular responses to short-term head-out water immersion in patients with chronic heart failure. J Cardiopulm Rehabil Prev. 2010;30(1):22-7.
36. Mourot L, Teffaha D, Bouhaddi M, Ounissi F, Vernochet P, Dugue B, et al. Training-induced increase in nitric oxide metabolites in chronic heart failure and coronary artery disease: an extra benefit of water-based exercises? Eur J Cardiovasc Prev Rehabil. 2009;16:215-21.
37. Vasić D, Novaković M, Božič Mijovski M, Barbič Žagar B, Jug B. Short-term water- and land-based exercise training comparably improve exercise capacity and vascular function in patients after a recent coronary event: A pilot randomized controlled trial. Front Physiol. 2019;10:903.
38. Jug B, Vasić D, Novaković M, Avbelj V, Lea R, Kšela J. The effect of aquatic exercise training on heart rate variability in patients with coronary artery disease. J Cardiovasc Dev Dis. 2022;9(8):251.

39. Teffaha D, Mourot L, Vernochet P, Ounissi F, Regnard J, Monpere C, et al. Relevance of water gymnastics in rehabilitation programs in patients with chronic heart failure or coronary artery disease with normal left ventricular function. J Card Fail. 2011;17:676-83.
40. Tokmakidis SP, Spassis AT, Volaklis KA. Training, detraining and retraining effects after a water-based exercise program in patients with coronary artery disease. Cardiology. 2008;111(4):257-64.
41. Volaklis K, Spassis A, Tomakadis S. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J. 2007;154:560.e1-.e6.
42. Fiogbé E, Ferreira R, Sindorf MAG, Tavares SA, de Souza KP, de Castro Cesar M, et al. Water exercise in coronary artery disease patients, effects on heart rate variability, and body composition: A randomized controlled trial. Physiother Res Int. 2018;23(3):1.
43. Lee J-Y, Joo K-C, Brubaker PH. Aqua walking as an alternative exercise modality during cardiac rehabilitation for coronary artery disease in older patients with lower extremity osteoarthritis. BMC Cardiovasc Disord. 2017;17(1):252.
44. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, Dalleck LC. Graded exercise testing protocols for the determination of VO2max: Historical perspectives, progress, and future considerations. J Sports Med. 2016;2016:3968393.
45. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J. 2008;156(2):292-300.
46. Scheer AS, Naylor LH, Gan SK, Charlesworth J, Benjanuvatra N, Green DJ, et al. The effects of water-based exercise training in people with type 2 diabetes. Med Sci Sports Exerc. 2020;52(2):417-24.
47. Tsourlou T, Benik A, Dipla K, Zafeiridis A, Kellis S. The effects of a twenty-four-week aquatic training program on muscular strength performance in healthy elderly women. J Strength Cond Res. 2006;20:811-8.
48. Barbat-Artigas S, Rolland Y, Cesari M, Abellan van Kan G, Vellas B, Aubertin-Leheudre M. Clinical relevance of different muscle strength indexes and functional impairment in women aged 75 years and older. J Gerontol A Biol Sci Med Sci. 2013;68(7):811-9.
49. Puthoff ML, Nielsen DH. Relationships among impairments in lower-extremity strength and power, functional limitations, and disability in older adults. Phys Ther. 2007;87(10):1334-47.
50. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851-63.
51. Medina-Inojosa JR, Somers VK, Thomas RJ, Jean N, Jenkins SM, Gomez-Ibarra MA, et al. Association between adiposity and lean mass with long-term cardiovascular events in patients with coronary artery disease: No paradox. J Am Heart Assoc. 2018;7(10):e007505.
52. Rothney MP, Martin F-P, Xia Y, Beaumont M, Davis C, Ergun D, et al. Precision of GE Lunar iDXA for the measurement of total and regional body composition in nonobese adults. J Clin Densitom. 2012;15(4):399-404.
53. Hind K, Oldroyd B, Truscott JG. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. Eur J Clin Nutr. 2011;65(1):140-2.
54. Dordevic AL, Bonham M, Ghasem-Zadeh A, Evans A, Barber E, Day K, et al. Reliability of compartmental body composition measures in weight-stable adults using GE iDXA: Implications for research and practice. Nutrients. 2018;10(10):1484.
55. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
56. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of atherosclerosis. Int J Mol Sci. 2022;23(6):3346.
57. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.
58. Matsuzawa Y, Kwon TG, Lennon Ryan J, Lerman Lilach O, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: A systematic review and meta-analysis. J Am Heart Assoc. 2015;4(11):e002270.
59. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Endothelial dysfunction, increased arterial stiffness, and cardiovascular risk prediction in patients with coronary artery disease: FMD-J (Flow-Mediated Dilation Japan) Study A. J Am Heart Assoc. 2018;7(14):e008588.
60. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000;342(7):454-60.

61. Manresa-Rocamora A, Ribeiro F, Casanova-Lizón A, Flatt AA, Sarabia JM, Moya-Ramón M. Cardiac rehabilitation improves endothelial function in coronary artery disease patients. Int J Sports Med. 2022;43(11):905-20.
62. Tinken T, Thijssen D, Hopkins N, Dawson E, Cable T, Green D. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension. 2010;55:312-8.
63. Carter HH, Cheng JL, MacDonald MJ, Pienaar O, Coleman A, Naylor LH, et al. The effects of exercise during water immersion on arterial function in humans. Am J Physiol Regul Integr Comp Physiol. 2023;324(4):R568-R73.
64. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559.
65. Anazodo UC, Shoemaker JK, Suskin N, St.Lawrence KS. An investigation of changes in regional gray mattter volume in cardiovascular disease patients, pre and post cardiovascular rehabilitation. Neuroimage Clin. 2013;3:388-95.
66. MacIntosh BJ, Swardfager W, Crane DE, Ranepura N, Saleem M, Oh PI, et al. Cardiopulmonary fitness correlates with regional cerebral grey matter perfusion and density in men with coronary artery disease. PLoS ONE. 2014;9(3):e91251.
67. Poirier SE, Suskin NG, Khaw AV, Thiessen JD, Shoemaker JK, Anazodo UC. Probing evidence of cerebral white matter microstructural disruptions in ischemic heart disease before and following cardiac rehabilitation: A diffusion tensor MR imaging study. J Magn Reson Imaging. 2023 (ePub).
68. Anazodo UC, Shoemaker JK, Suskin N, Ssali T, Wang DJJ, St. Lawrence KS. Impaired cerebrovascular function in coronary artery disease patients and recovery following cardiac rehabilitation. Front Aging Neurosci. 2016;7(224).
69. Coombs GB, Al-Khazraji BK, Suskin N, Shoemaker JK. Impact of ischemic heart disease and cardiac rehabilitation on cerebrovascular compliance. J Appl Physiol (1985). 2023;135(4):753-62.
70. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLoS One. 2017;12(9):e0184244-e.
71. Junejo RT, Braz ID, Lucas SJE, van Lieshout JJ, Phillips AA, Lip GYH, et al. Neurovascular coupling and cerebral autoregulation in atrial fibrillation. J Cereb Blood Flow Metab. 2019;40(8):1647-57.
72. Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. Am J Physiol Heart Circ Physiol. 2015;308(7):H681-H7.
73. Nowak-Flück D, Ainslie PN, Bain AR, Ahmed A, Wildfong KW, Morris LE, et al. Effect of healthy aging on cerebral blood flow, CO2 reactivity, and neurovascular coupling during exercise. J Appl Physiol. 2018;125(6):1917-30.
74. Girouard H, Iadecola C. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. J Appl Physiol. 2006;100(1):328-35.
75. Dabbaghipour N, Javaherian M, Moghadam BA. Effects of cardiac rehabilitation on cognitive impairments in patients with cardiovascular diseases: a systematic review. Int J Neurosci. 2020; 131(11):1124-1132.
76. Green D, Kurt. S, Maslen B, Cox K, Lautenshlager N, Pestell C, et al. The impact of six-month land versus water walking on cerebrovascular function in the aging brain. Med Sci Sports Exerc. 2021 53(10):2093-100.
77. Matsumoto I, Moriya S, Kurozumi M, Namba T, Takagi Y. Simultaneous evaluation of fatty acid and triglycerides after percutaneous coronary intervention. J Cardiol. 2022;80(2):149-54.
78. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111-88.
79. Grundy S, M., Stone N, J., Bailey A, L., Beam C, Birtcher K, K., Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019;73(24):e285-e350.
80. Virani SS, Smith SC, Stone NJ, Grundy SM. Secondary prevention for atherosclerotic cardiovascular disease. Circulation. 2020;141(14):1121-3.

81. Theodorou AA, Panayiotou G, Volaklis KA, Douda HT, Paschalis V, Nikolaidis MG, et al. Aerobic, resistance and combined training and detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery disease patients. Res Sports Med. 2016;24(3):171-84.
82. Ndrepepa G, Braun S, King L, Fusaro M, Keta D, Cassese S, et al. Relation of fibrinogen level with cardiovascular events in patients with coronary artery disease. Am J Cardiol. 2013;111(6):804-10.
83. Shitara J, Ogita M, Wada H, Tsuboi S, Endo H, Doi S, et al. Clinical impact of high-sensitivity C-reactive protein during follow-up on long-term adverse clinical outcomes in patients with coronary artery disease treated with percutaneous coronary intervention. J Cardiol. 2019; 73(1):45-50.
84. De Luca L, Cappadona F, Temporelli PL, Gonzini L, Ledda A, Raisaro A, et al. Impact of eGFR rate on 1-year all-cause mortality in patients with stable coronary artery disease. Eur J Intern Med. 2022;101:98-105.
85. Guimaraes GV, de Barros Cruz LG, Fernandes-Silva MM, Dorea EL, Bocchi EA. Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: A randomized controlled trial (HEx trial). Int J Cardiol. 2014;172(2):434-41.
86. Meyer K, Bücking J. Exercise in heart failure: should aqua therapy and swimming be allowed? Med Sci Sports Exerc. 2004;36(12):2017-23.
87. Grüner Sveälv B, Cider A, Täng MS, Angwald E, Kardassis D, Andersson B. Benefit of warm water immersion on biventricular function in patients with chronic heart failure. Cardiovasc Ultrasound. 2009;7:33.
88. Cider A, Sveälv BG, Täng MS, Schaufelberger M, Andersson B. Immersion in warm water induces improvement in cardiac function in patients with chronic heart failure. Eur J Heart Fail. 2006;8(3):308-13.
89. Adsett J, Morris N, Kuys S, Hwang R, Mullins R, Khatun M, et al. Aquatic exercise training is effective in maintaining exercise performance in trained heart failure patients: A randomised crossover pilot trial. Heart Lung Circ. 2017;26(6):572-9.
90. Caminiti G, Volterrani M, Marazzi G, Cerrito A, Massaro R, Sposato B, et al. Hydrotherapy added to endurance training versus endurance training alone in elderly patients with chronic heart failure: a randomized pilot study. Int J Cardiol. 2011;148:199-203.
91. Cider Å, Schaufelberger M, Stibrant Sunnerhagen K, Andersson B. Aquatic exercise is effective in improving exercise performance in patients with heart failure and type 2 diabetes mellitus. J Evid Based Complementary Altern Med. 2012;2012:8.
92. Campia U, Sullivan G, Bryant MB, Waclawiw MA, Quon MJ, Panza JA. Insulin impairs endothelium-dependent vasodilation independent of insulin sensitivity or lipid profile. Am J Physiol Heart Circ Physiol. 2004;286(1):H76-H82.
93. Parfitt R, Hensman MY, Lucas SJE. Cerebral blood flow responses to aquatic treadmill exercise. Med Sci Sports Exerc. 2017;49(7).
94. Carter HH, Spence AL, Pugh CJ, Ainslie P, Naylor LH, Green DJ. Cardiovascular responses to water immersion in humans: impact on cerebral perfusion. Am J Physiol Regul Integr Comp Physiol. 2014;306:R636-R40.
95. Pugh CJ, Sprung VS, Ono K, Spence AL, Thijssen DHJ, Carter HH, et al. The effect of water immersion during exercise on cerebral blood flow. Med Sci Sports Exerc. 2015;47(2):299-306.
96. Carter HH, Spence AL, Ainslie PN, Pugh CJA, Naylor LH, Green DJ. Differential impact of water immersion on arterial blood flow and shear stress in the carotid and brachial arteries of humans. Physiol Rep. 2017;5(10):e13285.
97. Mano T, Iwase S, Saito M, Koga I, Abe H, Inamura K, et al. Neural and humoral controlling mechanisms of cardiovascular functions in man under weightlessness simulated by water immersion. Acta Astronaut. 1991;23:31-3.
98. Ayme K, Gavarry O, Rossi P, Desruelle A-V, Regnard J, Boussuges A. Effect of head-out water immersion on vascular function in healthy subjects. Appl Physiol Nutr Metab. 2014;39(4):425-31.
99. Agewall S, Henareh L, Kublickiene K. Endothelial function in conduit and resistance arteries in men with coronary artery disease. Atherosclerosis. 2006;184:130-6.
100. Perdomo SJ, Ward J, Liu Y, Vidoni ED, Sisante JF, Kirkendoll K, et al. Cardiovascular disease risk is associated with middle cerebral artery blood flow velocity in older adults. Cardiopulm Phys Ther J. 2020;31(2):38-46.

101. Bérubé B, Boidin M, Gayda M, Vincent T, Tremblay J, Juneau M, et al. Acute effects of exercise on cerebrovascular response and cognitive performance in individuals with stable coronary heart disease. Brain Res. 2021:147671.
102. Gayda M, Gremeaux V, Bherer L, Juneau M, Drigny J, Dupuy O, et al. Cognitive function in patients with stable coronary heart disease: Related cerebrovascular and cardiovascular responses. PLoS One. 2017;12(9):e0183791.
103. Atkinson CL, Lewis NCS, Carter HH, Thijssen DHJ, Ainslie PN, Green DJ. Impact of sympathetic nervous system activity on post-exercise flow-mediated dilatation in humans. J Physiol. 2015;593(23):5145-56.
104. Miwa C, Mano T, Saito M, Iwase S, Matsukawa T, Sugiyama Y, et al. Ageing reduces sympatho-suppressive response to head-out water immersion in humans. Acta Physiol Scand. 1996;158(1):15-20.
105. Badrov MB, Wood KN, Lalande S, Sawicki CP, Borrell LJ, Barron CC, et al. Effects of 6 months of exercise-based cardiac rehabilitation on autonomic function and neuro-cardiovascular stress reactivity in coronary artery disease patients. J Am Heart Assoc. 2019;8(17):e012257.
106. Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular adaptation to exercise in humans: Role of Hemodynamic Stimuli. Physiol Rev. 2017;97(2):495-528.
107. Park KS, Choi JK, Park YS. Cardiovascular regulation during water immersion. Appl Human Sci. 1999;18(6):233-41.
108. Gabrielsen, VidebÆk, Johansen, Warberg, Christensen, Pump, et al. Forearm vascular and neuroendocrine responses to graded water immersion in humans. Acta Physiol Scand. 2000;169(2):87-94.
109. Hoiland RL, Caldwell HG, Carr JMJR, Howe CA, Stacey BS, Dawkins T, et al. Nitric oxide contributes to cerebrovascular shear-mediated dilatation but not steady-state cerebrovascular reactivity to carbon dioxide. J Physiol. 2022;600(6):1385-403.
110. Hoiland RL, Caldwell HG, Howe CA, Nowak-Flück D, Stacey BS, Bailey DM, et al. Nitric oxide is fundamental to neurovascular coupling in humans. J Physiol. 2020;598(21):4927-39.
111. Smirl JD, Wright AD, Bryk K, van Donkelaar P. Where's Waldo? The utility of a complicated visual search paradigm for transcranial Doppler-based assessments of neurovascular coupling. J Neurosci Methods. 2016;270:92-101.
112. Lapidaire W, Forkert ND, Williamson W, Huckstep O, Tan CM, Alsharqi M, et al. Aerobic exercise increases brain vessel lumen size and blood flow in young adults with elevated blood pressure. Secondary analysis of the TEPHRA randomized clinical trial. Neuroimage Clin. 2023;37:103337.
113. Thomas HJ, Rana U, Marsh CE, Caddy HT, Kelsey LJ, Smith KJ, et al. Assessment of cerebrovascular responses to physiological stimuli in identical twins using multimodal imaging and computational fluid dynamics. J Appl Physiol. 2020;129(5):1024-32.

APPENDICES

Appendix A Primary HREC approvals

A.1 Original application approval

Government of **Western Australia**
Department of **Health**
South Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee

4 December 2015

A/Prof Andrew Maiorana
Department of Allied Health
Fiona Stanley Hospital

Dear Andrew

Project Title: A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease
HREC Reference: REG 15-165

The ethics application for the project referenced above has been approved by the RPH Human Research Ethics Committee (HREC).

Approved documents:
Research Protocol 20 OCT 2015
Invitation Letter 20 OCT 2015
PICF Combined 20 OCT 2015
DASS 21 20 OCT 2015
Data Management Plan 20 OCT 2015
Flyer 20 OCT 2015
Food Diary 20 OCT 2015
IPAQ Short 7 Days 20 OCT 2015
Medications 20 OCT 2015
Screening Survey 20 OCT 2015
Training Program Exit Survey 20 OCT 2015

This approval is valid to **4 December 2018** and on the basis of compliance with the 'Conditions of HREC Approval for a Research Project' (attached).

The nominated participating site(s) in this project is/are:

- **Fiona Stanley Hospital**
- **Royal Perth Hospital**

If additional sites are recruited prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the HREC. Notification of withdrawn sites should also be provided to the HREC in a timely fashion.

This letter constitutes ethical approval only. This project cannot proceed at any site until separate site authorisation has been obtained from the CE, or delegate, of the site following Site Specific Assessment by a Research Governance Officer.

The RPH HREC is registered with the Australian Health Ethics Committee and operates according to the NHMRC National Statement on Ethical Conduct in Human Research and International Conference on Harmonisation – Good Clinical Practice.

Southern Integrated Research Organisation (SIRO)
Locked Bag 100, PALMYRA DC WA 6961
Telephone: 08 6151 1180
Email: SMHS.REG@health.wa.gov.au
www.southmetropolitan.health.wa.gov.au

Should you have any queries about the HREC's consideration of your project, please contact the HREC Administrative Officer on 6151 1180. The HREC's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the SIRO Research Ethics & Governance Unit or from the website http://smhs.hdwa.health.wa.gov.au/ServicesFacilitiesLocator/sa/ethics/aboutus.asp?v=0.
Yours sincerely

[redacted]

PROF FRANK VAN BOCKXMEER
CHAIRMAN ROYAL PERTH HOSPITAL HUMAN RESEARCH ETHICS COMMITTEE

A.2 Amendment approval May 2016

Government of **Western Australia**
Department of **Health**
South Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee (EC00270)

26 May 2016

Assoc Professor Andrew Maiorana
Allied Health, FSH
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH WA 6150

Dear Assoc Professor Maiorana

Project Title: ***A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease***
REG Number: **2015-165**

The following **amendments** have been **approved** by the Royal Perth Hospital Human Research Ethics Committee:

Documents
Research protocol Version 3, 10 May 2016 Scheer Combined PICF Version 3, 10 May 2016 Addition of personnel: Dr Amit Shah, Advanced Heart Failure & Cardiac Transplant Service FSH - additional Cardiology expertise to support project and contribute to data interpretation. Dr Kurt Smith, School of Sports Science UWA - Experience researcher with skills in vascular and transcranial Soppler ultrasound.

South Metropolitan Health Service Site Governance approval will be forthcoming.

Please submit a copy of this approval letter to the Research Governance Office at each **non** SMHS site.

Yours sincerely

[redacted]

MR HAMISH MILNE
A/Chairman | Royal Perth Hospital Human Research Ethics Committee

Southern Integrated Research Organisation (SIRO)
Locked Bag 100, PALMYRA DC WA 6961
Telephone: 08 6151 1180
Email: SMHS.REG@health.wa.gov.au
www.southmetropolitan.health.wa.gov.au

A.3 Amendment approval October 2016

Government of Western Australia
East Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee (EC00270)

27 October 2016

Assoc Professor Andrew Maiorana
Advanced Heart Failure & Cardiac Transplant Service
Fiona Stanley Hospital

Dear Assoc Professor Maiorana

Project Title: ***A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease***
REG Number: **2015-165**

The following **amendment/s (and associated documents)** were **approved** by the Royal Perth Hospital Human Research Ethics Committee at its **26 October 2016** meeting:

Documents
Research Protocol Version 4, dated 2 September 2016
Summary of Changes Letter dated 2 September 2016
Scheer Combined PICF Version 4, dated 2 September 2016
Screening Survey - Coronary Heart Disease and Exercise Study

Governance approval for East Metropolitan Health Service (EMHS) sites will be forthcoming.

Please submit a copy of this approval letter to the Research Governance Office at each non-EMHS site.

Yours sincerely

[redacted]

DR RAMIN GHARBI
Chairman | Royal Perth Hospital Human Research Ethics Committee

CC: Anna Scheer

Research Ethics & Governance
Level 3 Colonial House, Royal Perth Hospital, GPO Box X2213 Perth WA 6847
Telephone: (08) 9224 2260 / (08) 9224 2292
Email: EMHS.REG@health.wa.gov.au

A.4 Amendment approval March 2017

Government of Western Australia
East Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee (EC00270)

23 March 2017

Assoc Professor Andrew Maiorana
Advanced Heart Failure & Cardiac Transplant Service
Fiona Stanley Hospital

Dear Assoc Professor Maiorana

Project Title: ***A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease***
REG Number: **2015-165**

The following **amendment/s (and associated documents)** were **approved** by the Royal Perth Hospital Human Research Ethics Committee at its **22 March 2017** meeting:

Documents
Research Protocol Version 5 (08/02/2017)
Advertising Flyer 2 Version 1 (12/01/2017)
Radio Advertisement Version 1 (12/01/2017)
Curtin University Newspaper Advertisement Version 1 (23/02/2017)
DEXA Scheer Oct 2016 Revised Jan 2017 Version 2 (25/01/2017)
Email to groups Version 1 (12/01/2017)

Governance approval for East Metropolitan Health Service (EMHS) sites will be forthcoming.

Please submit a copy of this approval letter to the Research Governance Office at each non-EMHS site.

Yours sincerely

[redacted]

DR RAMIN GHARBI
Chairman | Royal Perth Hospital Human Research Ethics Committee

Cc: Anna Scheer

Research Ethics & Governance
Level 2 Kirkman House, Royal Perth Hospital, GPO Box X2213 Perth WA 6847
Telephone: (08) 9224 2260 / (08) 9224 2292
Email: EMHS.REG@health.wa.gov.au

Appendix B Curtin University reciprocal approvals

B.5 Original reciprocal approval

MEMORANDUM

Curtin University

To:	A/Prof Andrew Maiorana School of Physiotherapy and Exercise Science
CC:	
From	Professor Peter O'Leary, Chair HREC
Subject	Reciprocal ethics approval Approval number: HR227/2015
Date	11-Dec-15

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for your application submitted to the Human Research Ethics Office for the project: 6232

A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease

Your application has been approved through Curtin University Human Research Ethics Committee (HREC) through a reciprocal approval process with the lead HREC.

The lead HREC for this project has been identified as RPH Human Research Ethics Committee

Approval number from the lead HREC is noted as: REG 15-165

Please note the following conditions of approval:

1. Approval is granted from **15-Dec-15** to **04-Dec-18**
2. Research must be conducted as stated in the approved protocol.
3. Any amendments to the approved protocol must be approved by the Ethics Office.
4. An annual progress report must be submitted to the Ethics Office annually, on the anniversary of approval.
5. All adverse events must be reported to the Ethics Office.
6. A completion report must be submitted to the Ethics Office on completion of the project.
7. Data must be stored in accordance with WAUSDA and Curtin University policy.
8. The Ethics Office may conduct a randomly identified audit of a proportion of research projects approved by the HREC.

Should you have any queries about the consideration of your project please contact the Ethics Support Officer for your faculty, or the Ethics Office at hrec@curtin.edu.au or on 9266 2784. All human research ethics forms and guidelines are available on the ethics website.

Yours sincerely

[redacted]

Professor Peter O'Leary
Chair, Human Research Ethics Committee

B.6 May 2016 reciprocal approval

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

30-May-2016

Name: Andrew Maiorana
Department/School: School of Physiotherapy and Exercise Science
Email: A.Maiorana@curtin.edu.au

Dear Andrew Maiorana

RE: Amendment approval
Approval number: HR227/2015

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HR227/2015-01 approved on 30-May-2016.

The following amendments were approved:

Research protocol version 3, 10 May 2016.

Scheer Combined PICF version 3, 10 May 2016.

Addition of personnel:

Dr Amit Shah and Dr Kurt Smith

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)

4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

Professor Peter O'Leary
Chair, Human Research Ethics Committee

B.7 October 2016 reciprocal approval

Curtin University

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

28-Oct-2016

Name: Andrew Maiorana
Department/School: School of Physiotherapy and Exercise Science
Email: A.Maiorana@curtin.edu.au

Dear Andrew Maiorana

RE: Amendment approval
Approval number: HR227/2015

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HR227/2015-02 approved on 28-Oct-2016.

The following amendments were approved:

This amendment has been approved by RPH HREC on the 27/10/2016.

1. We have split one testing session in Study B into 2 sessions and have moved the brain blood flow testing to UWA.

2. We are including dual energy X-ray absorptiometry (DEXA) scans for body composition (very low dose X-ray).

3. We are including physical activity monitoring with a non-invasive wearable device for 1 week pre and post study.

4. We are including a brief familiarisation session for the cognitive testing session at the vascular function testing session.

5. We have added questions to the screening questions list to ensure participants meet the entry criteria for the hydrotherapy pool at Fiona Stanley Hospital.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project

- major deviations from the approved proposal and/or regulatory guidelines
- serious adverse events

3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

Professor Peter O'Leary
Chair, Human Research Ethics Committee

B.8 March 2017 reciprocal approval

Curtin University

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

05-Apr-2017

Name: Andrew Maiorana
Department/School: School of Physiotherapy and Exercise Science
Email: A.Maiorana@curtin.edu.au

Dear Andrew Maiorana

RE: Amendment approval
Approval number: HR227/2015

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease.**

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HR227/2015-04 approved on 05-Apr-2017.

The following amendments were approved:
We have included additional advertising strategies - such as radio, newspaper advertising and flyers. We have included an updated DEXA radiation dose letter. We have clarified in the protocol that we are not excluding all people with diabetes from taking part in this study, only those taking insulin and we have added chronic obstructive pulmonary disease (COPD) as an exclusion

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project

7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Dr Catherine Gangell
Manager, Research Integrity

Appendix C University of Western Australia reciprocal approval

THE UNIVERSITY OF WESTERN AUSTRALIA

Human Ethics
Office of Research Enterprise
The University of Western Australia
M459, 35 Stirling Highway
Crawley WA 6009 Australia
T +61 8 6488 3703 / 4703
F +61 8 6488 8775
E humanethics@uwa.edu.au
CRICOS Provider Code 00126G

Our Ref: RA/4/1/8382

07 June 2016

Dr Andrew Maiorana

Dear Doctor Maiorana

HUMAN RESEARCH ETHICS OFFICE – NOTIFICATION OF ETHICS APPROVAL FROM ANOTHER ETHICS COMMITTEE

Project: A Randomised, Controlled Trial of Water-Based Exercise Training in People with Stable Coronary Heart Disease - Recognition Royal Perth Hospital HREC Approval REG 15-165

Thank you for your correspondence notifying this office of your project's review and approval by a non-UWA Research Ethics Committee.

It is noted that you have ethics approval from Royal Perth Hospital, approval number REG 15-165.

The students and researchers identified as working on this project are:

Name	*Faculty / School*	*Role*
Dr Andrew Maiorana	Royal Perth Hospital	Chief Investigator
Dr Louise Naylor	School of Sport Science, Exercise and Health	Co-Investigator
Dr Kurt Smith	School of Sport Science, Exercise and Health	Co-Investigator
Professor Carl Schultz	WA Department of Health	Co-Investigator
Anna Scheer	Curtin University of Technology	Co-Investigator
Dr Beatriz de Oliveira	Curtin University of Technology	Co-Investigator
Dr Nik Stoyanov	WA Department of Health	Co-Investigator
Dr Amit Shah	WA Department of Health	Co-Investigator
Winthrop Professor Daniel Green	School of Sport Science, Exercise and Health	Co-Investigator

Although The University of Western Australia reserves the right to subject any research involving its staff and students to its own ethics review process, in this case, the UWA Human Ethics Office recognizes the existing approval of the non-UWA ethics committee.

1. *Approving HREC to receive annual reports, amendments and notification of adverse events*

You are reminded that the approving ethics committee remains the monitoring committee for this project. You must correspond with them for matters regarding amendments, adverse events, annual and final reporting.

If you have any queries, please contact the HEO at humanethics@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/8382 – and the associated project title in all future correspondence.

Yours sincerely

[redacted]

Dr Caixia Li
Manager, Human Ethics

Appendix D Governance approvals

D.9 Fiona Stanley Hospital initial approval

Government of **Western Australia**
Department of **Health**

FIONA STANLEY hospital

Enquiries : (08) 6151 1180

Associate Professor Andrew Maiorana
Advanced Heart Failure
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH WA 6150

Dear Associate Professor Maiorana

Project Title: A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease
Protocol: Version 3 dated 10 May 2016
HREC Reference: 2015-165

On behalf of Fiona Stanley Hospital, I give authorisation for your research project to be conducted at Fiona Stanley Hospital.

The documents approved for use at site are those approved by the HREC in the letters dated 4 December 2015 and 26 May 2016 :

Approved document(s)
• Combined Participant Information and Consent Form Version 3, dated 10 May 2016

This authorisation is based on the approval from the Royal Perth Hospital Human Research Ethics Committee and the review from the Research Governance Office. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' (attached) and with the compliance of all reports as required by the Research Governance Office and approving HREC. Noncompliance with these requirements could result in the authorisation being withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

Yours sincerely

[redacted]

Karen McMenamin
A/EXECUTIVE DIRECTOR

July 2016

11 Robin Warren Drive
Murdoch WA 6150
Telephone: (08) 6152 2222

Locked Bag 100
Palmyra DC, WA 6961
www.fsh.health.wa.gov.au

D.10 Fiona Stanley Hospital amendment approval

05/05/2017

Dear Assoc Professor Maiorana

Project Title:	**A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease**
Protocol:	
Ref Number:	**2015-165**
HREC:	**Royal Perth Hospital**
SMHS site:	**Fiona Stanley Hospital**

The following amendment/s have been approved by the SMHS site:

Amendment/Documents
• 20170112_Flyer 2_version 1 (10/01/2017) • 20170112_Radio Advertisement _version 1 (10/01/2017) • 20170223_Curtin University Newspaper Advertisement_ version 1 (23/02/2017) • 20170112_Email to groups_ version 1 (10/01/2017) • 20161019_DEXA Scheer Oct 2016 Revised Jan 2017_version 2 (25/01/2017) • 20170208_Research protocol_ version 5 (08/02/2017) • 20170223_Summary of Changes (23/02/2017)

Please keep a copy of this email as evidence of site research governance approval.

Kind regards

Selina

Selina Metternick-Jones | Compliance Monitoring and Education Officer
South Metropolitan Health Service Fiona Stanley Hospital
Level 3, Harry Perkins Institute of Medical Research,Fiona Stanley Hospital, 11 Robin Warren Drive, MURDOCH WA 6150.

D.11 Royal Perth Hospital initial approval

Government of Western Australia
Department of Health
South Metropolitan Health Service

21 June 2016

Andrew Maiorana
Exercise Physiology Professional Lead
Allied Health Department
Fiona Stanley Hospital

Dear Andrew

Project Title: Project_A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease
Protocol No: Version 3 dated 10 May 2016
HREC Reference: 15-165

On behalf of Royal Perth Hospital, I give authorisation for your research project to be conducted at Royal Perth Hospital

The documents approved for use at site are those listed in the RPH HREC Approval letter dated 04 Dec 2015 and 26 May 2016.

Approved document(s)
Research Protocol Version 3, 10 May 2016 Scheer Combined PICF Version 3, 10 May 2016

This authorisation is based on the approval from the Royal Perth Hospital Human Research Ethics Committee and the review from the Research Governance Office. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' (attached) and with the compliance of all reports as required by the Research Governance Office and approving HREC. Noncompliance with these requirements could result in the authorisation being withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

Yours sincerely

[redacted]

Dr Aresh Anwar
EXECUTIVE DIRECTOR

D.12 Royal Perth Hospital amendment approval

Government of Western Australia
East Metropolitan Health Service

27 March 2017

Assoc Professor Andrew Maiorana
Advanced Heart Failure & Cardiac Transplant Service
Fiona Stanley Hospital

Dear A/Professor Maiorana

Project Title: A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease
HREC Reference: 2015-165

On behalf of Royal Perth Hospital, East Metropolitan Health Service I give authorisation for the amendment to the above project to be implemented at Royal Perth Hospital.

The following **amendment/s (and associated documents)** have been approved:

- Research Protocol Version 5 (08/02/2017)
- Advertising Flyer 2 Version 1 (12/01/2017 for RPH site)
- Radio Advertisement Version 1 (12/01/2017)
- Curtin University Newspaper Advertisement Version 1 (23/02/2017)
- DEXA Scheer Oct 2016 Revised Jan 2017 Version 2 (25/01/2017)
- Email to groups Version 1 (12/01/2017)

This authorisation is based on compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' and with the compliance of all reports as required by the Research Governance Office and approving HREC.

Non-compliance with these requirements could result in the authorisation being withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site/s.

A copy of this letter should be given to the CPI to enable accurate coordination of the conduct of the project.

Yours sincerely

[redacted]

Dr Aresh Anwar
EXECUTIVE DIRECTOR

CC: Anna Scheer

Research Ethics & Governance
Level 2 Kirkman House, Royal Perth Hospital, GPO Box X2213 Perth WA 6847
Telephone: (08) 9224 2260 / (08) 9224 2292
Email: EMHS.REG@health.wa.gov.au

D.13 Estimated effective doses for radiographic procedures (initial)

THE UNIVERSITY OF WESTERN AUSTRALIA

Safety and Health Office

The University of Western Australia
35 Stirling Highway
Crawley WA 6009

Phone +61 8 9380 7932
Fax +61 8 9380 1179
Email [redacted]
Web http://www.safety.uwa.edu.au

Kate Kirk
Administrative Officer
Human Research Ethics Committee
University of Western Australia
Crawly, WA, 6009

19th October 2016

Estimated Effective Doses for Radiographic Procedures

School: UWA School of Sport Science, Exercise and Health

Project Title: A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease

Chief Investigators: W/Prof Daniel Green, A/Prof Andrew Maiorana, Dr Beatriz IR de Oliveira, Anna Scheer

X-ray procedures:

Total body scan – 2 scans per participant, before and after a 12 week intervention programme so to determine lean body mass and fat mass. The scan will consist of a full body composition scan. 60 adult participants (aged over 18) will be recruited. Start date: November, 2016 or later depending on ethics approval being granted.

- Scanning will be carried out once ethics approval has been received and will continue until approximately February, 2018.
- All study participants will be volunteers.
- All participants will be adults with stable coronary heart disease.
- Informed consent will be obtained from all participants prior to scanning.

Radiation License details:

Licensee Name: Prof Tim Ackland License No. [redacted]
School of Sport Science, Exercise and Health
The University of Western Australia

Only trained operators will have permission to use the x-ray machine. A software password system is available on the machine to prevent unauthorized use. The training course is a half-day regulator approved course and trained operators have received certification for operation of the machine.

Machine data from manufacturer's literature

From:	Operator's Guide
X-ray machine:	Lunar prodigy
X-ray beam:	76kV, 2.9mmAl at 70kVp, focal spot 0.5 mm. Max 76 kV, 3 mA Focal spot to image receptor distance 67 cm Table attenuation 0.7 mm Al

Summary:

A total body (thick) scan has a calculated effective dose of 0.8 µSv. Total dose is 1.6 µSv.

The patient consent form will state the estimated effective dose and place the radiation dose into a context understandable by all parties. The effective dose may be compared to that which is received from natural background sources eg.

"The tests involve the use of a low dose x-rays about equal to one thousandth of the background radiation you would receive in one year living in Perth. The total background radiation in Western Australia is about 2mSv per year. The radiation dose from cosmic rays from flying in a jet from Perth to London is approximately 0.1 mSv."

The hypothetical risk of developing cancer from the radiation exposure may be calculated using the ICRP 103 risk factor of 5%/Sv (Table 1, p.53). For participation in the complete procedure the fatal cancer risk is $(1.6 \times 10^{-6}) \times (5 \times 10^{-2}) = 4 \times 10^{-8} = 8$ in one hundred million.

Since the estimated effective dose to patients will be much less than 5 mSv in a year, a submission to the West Australian Radiological Council for approval is not required.

Yours faithfully

[redacted]

Jonathon Thwaites
Radiation and Safety Officer

Cc: Prof Tim Ackland

References:

ICRP 103. 2007. Recommendations of the international commission on radiological protection.

Shleien, B (ed). 1992. The health physics and radiological health handbook, Revised Edition. Scinta, Inc.

D.14 Estimated effective doses for radiographic procedures (second)

Safety and Health Office

The University of Western Australia
35 Stirling Highway
Crawley WA 6009

Phone +61 8 9380 7932
Fax +61 8 9380 1179
Email [redacted]
Web http://www.safety.uwa.edu.au

Kate Kirk
Administrative Officer
Human Research Ethics Committee
University of Western Australia
Crawly, WA, 6009

25th January 2017

Estimated Effective Doses for Radiographic Procedures

School: UWA School of Sport Science, Exercise and Health

Project Title: A randomised, controlled trial of water-based exercise training in people with stable coronary heart disease

Chief Investigators: W/Prof Daniel Green, A/Prof Andrew Maiorana, Dr Beatriz IR de Oliveira, Anna Scheer

X-ray procedures:

Total body scan – 2 scans per participant, before and after a 12 week intervention programme so to determine lean body mass and fat mass. The scan will consist of a full body composition scan. 60 adult participants (aged over 18) will be recruited. Start date: November, 2016 or later depending on ethics approval being granted.

- Scanning will be carried out once ethics approval has been received and will continue until approximately February, 2018.
- All study participants will be volunteers.
- All participants will be adults with stable coronary heart disease.
- Informed consent will be obtained from all participants prior to scanning.

Radiation License details:

Licensee Name: Prof Tim Ackland License No. [redacted]
School of Sport Science, Exercise and Health
The University of Western Australia

Only trained operators will have permission to use the x-ray machine. A software password system is available on the machine to prevent unauthorized use. The training course is a half-day regulator approved course and trained operators have received certification for operation of the machine.

Machine data from manufacturer's literature

From: Operator's Guide
X-ray machine: GE Lunar iDXA, sn ME+210760

Summary:

A total body (thick) scan has a calculated effective dose of 6 µSv. Total dose is 12 µSv.

The patient consent form will state the estimated effective dose and place the radiation dose into a context understandable by all parties. The effective dose may be compared to that which is received from natural background sources eg.

"The tests involve the use of a low dose x-rays about equal to one thousandth of the background radiation you would receive in one year living in Perth. The total background radiation in Western Australia is about 2mSv per year. The radiation dose from cosmic rays from flying in a jet from Perth to London is approximately 0.1 mSv."

The hypothetical risk of developing cancer from the radiation exposure may be calculated using the ICRP 103 risk factor of 5%/Sv (Table 1, p.53). For participation in the complete procedure the fatal cancer risk is $(12 \times 10^{-6}) \times (5 \times 10^{-2}) = 0.6 \times 10^{-6} = 6$ in ten million

Since the estimated effective dose to patients will be much less than 5 mSv in a year, a submission to the West Australian Radiological Council for approval is not required.

Yours faithfully

[redacted]

Jonathon Thwaites
Radiation and Safety Officer

Cc: Prof Tim Ackland

References:

ICRP 103. 2007. Recommendations of the international commission on radiological protection.

Shleien, B (ed). 1992. The health physics and radiological health handbook, Revised Edition. Scinta, Inc.

Appendix E Participant information sheet and consent forms

E.15 Participant information sheet and consent form Version 3

This was the first version for use with potential participants approved May 2016.

Government of Western Australia
Department of Health

PARTICIPANT INFORMATION SHEET

A Randomised, Controlled Trial of Water-Based Exercise in People with Stable Coronary Heart Disease:

Principal Investigator: Associate Professor Andrew Maiorana
Associate Investigators: Professor Carl Schultz, Dr. Nik Stoyanov, Ms. Anna Scheer, Dr. Beatriz IR de Oliveira, Winthrop Professor Daniel Green, Dr. Louise Naylor, Dr. Kurt Smith, Dr. Amit Shah

Fiona Stanley Hospital (FSH), Royal Perth Hospital (RPH), The University of Western Australia and Curtin University are undertaking a study to compare the effects of different types of exercise for people who have a heart condition called coronary heart disease (CHD). *You are being invited to participate in this research study because you are being treated for CHD at FSH or RPH.* Please read the information about this study carefully and ask any questions you might have. You may also wish to discuss the study with a relative, friend or your GP.

Background and aim
Regular exercise has been found to improve the health of people with CHD and reduce the chance of experiencing further heart problems. However many people with CHD do not do enough exercise to receive these benefits. One of the reasons for this may be that the typical forms of exercise prescribed to people with heart conditions do not suit them.

This study will investigate if a new type of water-based exercise, which might be more attractive to people with CHD, is as effective as traditional gym-based exercise for people with CHD. In order to do this we plan to observe the short and medium term effects of water-based exercise compared to gym-based exercise and normal activities.

There are two parts to this research (Study A and Study B) and you can participate in one or both of these. Study A involves an endurance capacity assessment and a one-off exercise session comparing low and moderate intensity exercise on land and in the water. Study B will look at the effects of gym or water-based exercise training on fitness, strength, body composition, brain and arm blood flow and blood vessel function, memory, and blood test results (cholesterol and inflammatory markers).

Study A

What participation in Study A will involve
If you decide to participate, we ask you to attend one testing session for endurance capacity and one exercise session.

Session 1: Endurance capacity (*Location:* **FSH or RPH***; Expected Duration:* **1 hour)**

Your breathing will be measured while you walk or jog on a treadmill. The speed and steepness of the slope will be progressively increased until you get too tired to continue in order to determine your fitness. The test will require you to breathe into a mouthpiece/mask as you do the test so the air you exhale can be analysed.

Heart rate and rhythm will be continuously monitored throughout the test and testing will be stopped immediately if any adverse changes occur. This test is used to determine how well your body can deliver and use oxygen and the fitness of your heart and lungs.

Session 2: Exercise session (*Location:* **UWA**; *Expected Duration:* **2.5 hours)**

We will ask you to fast for 6 hours before attending this test (meaning you won't be able to eat or consume caffeine for this time).

On arrival, you will be set up with the same mouthpiece/mask as for the endurance capacity assessment so we can monitor your breathing and how hard you are exercising during this session.

There will also be several other pieces of equipment to set-up prior to the exercise. These will allow us to measure blood flow to your arm and brain, along with assessing heart rate and body temperatures.

- We will place a small thermometer in your ear to measure changes in your core temperature with exercise.
- We will affix small skin thermometers to your arm and chest to measure temperature during the exercise.
- We will put a head frame that resembles a bike helmet on your head to keep two ultrasound probes steady. These probes will measure blood flow going to your brain.
- We will ask you to wear the mask you wore for the endurance capacity test so we can determine the level of exercise that you are working at.
- Finally, we will also use an ultrasound machine (similar to the machines used to look at unborn babies) to look at an artery in your arm and arteries in your neck during the session. We will monitor your blood pressure and heart rate using a small cuff around your finger during the session.

Once you are all set up we will randomly allocate you (as if by the toss of a coin) to complete either the water-based or land-based exercise *first*.

- The **water-based ('wet') exercise** involves standing in a pool up to the level of your lower chest, with your arms resting on a platform.

- The **land-based ('dry') exercise** also involves standing with your arms resting on a platform.

For each condition (wet and dry) we will get you to stand still for 10 minutes while we obtain 'baseline' measurements from the various monitors. We will then ask you to do a maximum squeeze with your hand so we can work out what your maximum hand grip strength is. Next we will ask you to hold a squeeze at 40% of this maximum until you can no longer maintain this strength of squeeze because your hand muscles get tired (this will take about 3 minutes). We will then inflate a blood pressure cuff on your forearm for 5 minutes. Your hand and forearm muscles may feel tired while doing the squeezing exercise, or you may experience some numbness while the cuff is inflated but both these feelings will resolve quickly once the exercise is stopped and the cuff deflated. If at any stage you wish to stop

the squeezing exercise or have the cuff deflated notify the researcher doing the procedure and this will occur.

During these procedures we will be measuring the blood flow to the brain (with the headframe that will already be set up) and the blood flow in your neck (using ultrasound). During exercise you breathe faster, which can lower the concentration of carbon dioxide in your body, which can effect some of the measurements we will be doing during the handgrip test. To counteract this, we will ask you to breathe in a concentration of carbon dioxide that is slightly higher than normal air (1-2% compared with 0.04%) to bring the carbon dioxide levels in your blood back to resting levels. After this we will ask you to exercise (marching on the spot) at a low intensity for 5 minutes, followed by a moderate intensity (increase in breathing and heart rate, but still able to talk normally) for 5 minutes. Then we will ask you to rest for 5 minutes in the standing position and do another handgrip 'squeezing' test like the one described above.

Between the two conditions (wet and dry) we will ask you to sit down and rest for 15-20 minutes.

Study B

What participation in Study B will involve
If you decide to participate in this study you will be:

- Randomly allocated to either water-based training, gym-based training or usual activities
- Asked to participate in testing sessions before and after completing whichever activity you are allocated to.
- A small number of people in each of the training groups will also be asked to come 20 minutes early to training once per fortnight to use the ultrasound machine to look at an artery in the arm before training. This will involve a blood pressure cuff being inflated on the forearm, as described for testing session 2.

If you are in the training groups you will be asked to complete 3 **training sessions per week**, lasting for **1 hour and 10 minutes** each for **12 weeks**. These sessions will incorporate a warm up, cool down, and circuit training, with both endurance and strength exercises. Each station will last for 90 seconds. The endurance stations will work on building your heart and lung fitness and the strengthening stations will work on your muscle strength. All exercises will be maintained at a moderate intensity but will start at an easier level and get slightly harder as you get used to the exercises.

If you are in the usual activities group we will ask you to maintain the same level of activity as before the study for 12 weeks and we will offer you an optional training program at the end of the study.

Testing session 1:
(*Location:* **FSH or RPH***; Expected Duration:* **2 hours)**
This will involve the following tests**);**

Endurance capacity - The same as Study A.

Muscle strength - We will look at the strength of some muscles in your arms and legs using machines in the gym. We will firstly get you to move a light weight 6 times to warm up and then we will make the weight heavier for a single lift at a time, until it is too heavy for you to lift.

Body composition - We will weigh you on a set of scales and measure around your waist and hips with a tape measure. We will also measure your height.

Blood test - this involves a standard blood test, where blood is taken from the arm and can be done at the end of this session, or at any time convenient to you at a PathWest branch. This will look at cholesterol, electrolyte levels and inflammatory markers. The samples will only be used for this project and any left over at the end of the project will be destroyed.

Testing session 2:
(*Location:* **FSH or RPH***; Expected Duration:* **2 hours)**
With this session we will ask you to fast for 6 hours before coming in for testing and to abstain from vigorous exercise, caffeine and alcohol for 24 hours before the study.

This will involve the following tests:

Blood vessel function - An ultrasound machine will be used to determine the diameter and blood flow of a large artery of the arm. After images are taken, a blood pressure cuff will be put on your forearm and pumped up for 5 minutes. This may feel slightly uncomfortable and you may experience numbness in your hand and fingers, however this should quickly resolve when the cuff is deflated.

After this we will use the ultrasound machine again to look at how the artery in your arm responds to a dose of a medicine called glyceryl trinitrate. This is commonly used to treat angina and it increases blood flow through the arteries. This drug can sometimes give people a headache and make them feel dizzy. We will take your blood pressure before this and not administer the drug if it is too low to try and avoid any dizziness. Should a headache occur it can be treated with Panadol.

The ultrasound machine will also be used to look at the thickness of an artery in your neck.

Brain blood flow - A special type of ultrasound machine will be used to look at some arteries going to the brain to determine the rate of blood flow to the brain. The probes from this ultrasound machine will be mounted on a head frame, and will sit above and in front of the ears. We will take some measurements with you resting and then we will get you to look at a computer screen. The screen will show a chessboard that changes colours for periods of time. We do this so we can see what happens to the blood flow to a part of the brain. We will also ask you to sit down and stand up several times. This is so we can see how well the brain copes with changes in blood pressure.

Memory and reaction speed - we will ask you to take part in a computer test where you click the right and left buttons on the mouse in response to what the computer program tells you.

Mood questionnaire - Before the memory and reaction speed tests, we will ask you to fill out a questionnaire about your mood by circling boxes on a form. This asks questions about your feelings and emotions over the preceding week. *If the researcher administering the questionnaires identifies that your mental health is being significantly impacted by your heart*

condition, we will advise you and offer you a referral to a Psychiatrist or Clinical Psychologist for follow up.

Systemic haemodynamics - blood pressure, heart rate and cardiac output will be measured using a technique that involves placing a small blood pressure cuff around a finger. This finger may feel slightly numb and change colour while the cuff is on, but resolves once the cuff is deflated.

Possible side effects and risks
The risk of an adverse event with exercise testing and training is low and regular physical activity and exercise are recommended to maintain good health. The incidence of major complications occurring with exercise testing has been found to be less than 1 per 10000 tests. Rigorous screening will be undertaken prior to any exercise *and you will be carefully monitored by appropriately trained staff at all times to ensure your safety*. Staff supervising exercise sessions will be trained in first aid and a protocol will be in place for any medical emergencies. There is also a risk you may experience some delayed onset muscle soreness after exercise testing, however this should resolve within 48-72 hours.

Possible benefits
Participation in this study will provide you with a supervised exercise program designed to improve your strength and fitness. In addition, the results of the study may help with better management of CHD in the future.

Privacy and Confidentiality
The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with the Privacy Act 1988. Your research data will initially be identified only by a unique study code and held separately from a link that matches the code to your name. No identifiable data (e.g., with your name attached) will leave FSH. Once the study is completed, the data will be anonymised, by deleting the link that matches the code to your name. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

What if something goes wrong?
In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Fiona Stanley Hospital.

Costs to participation
There will be no costs incurred as a result of participation in this study. You will not be paid for participation but reimbursement for expenses you incur associated with travel and parking to attend study specific visits will be available.

Voluntary participation and withdrawal from the project
Participation in this study is entirely voluntary. Your decision to participate or not will in no way affect your current or future care at Royal Perth Hospital or Fiona Stanley Hospital. You are also free to withdraw from the study at any time without reason or justification. If you decide to withdraw from the study, you can request removal of the data collected about you up to that point.

Contacts for further information
If you have questions about this study, please contact Anna Scheer on (08) [redacted] or via email [redacted] This study has been approved by the Curtin University and Royal Perth Hospital Human Research Ethics Committees. If you have any concerns about the conduct of the study or your rights as a research participant, please contact the South Metropolitan Health Service Research Ethics and Governance Unit on (08) 6151 1180 or email SMHS.REG@health.wa.gov.au and quote the ethics approval number (15-165).

CONSENT FORM

A Randomised, Controlled Trial of Water-Based Exercise in People with Stable Coronary Heart Disease:

Study A- Acute Effects of Water-Based Exercise

Principal Investigator: Dr Andrew Maiorana, Cardiac Transplant Service, FSH

I, ... agree to participate in the above study. I have read and understood the attached information sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the Investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

Signed _____ **Date** _____

Signature _____ **Date** _____

of person obtaining consent

Name _____

of person obtaining consent

CONSENT FORM

A Randomised, Controlled Trial of Water-Based Exercise in People with Stable Coronary Heart Disease:

Study B - Exercise Training

Principal Investigator: Dr Andrew Maiorana, Cardiac Transplant Service, FSH

I, ... agree to participate in the above study. I have read and understood the attached information sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the Investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

Signed _____ **Date** _____

Signature _____ **Date** _____

of person obtaining consent

Name _____

of person obtaining consent

E.16 Participant information sheet and consent form Version 4

The pages with changes have been tracked and included below (Oct 2016).

Body composition - We will weigh you on a set of scales and measure around your waist and hips with a tape measure. We will also measure your height.

Blood test - this involves a standard blood test, where blood is taken from the arm and can be done at the end of this session, or at any time convenient to you at a PathWest branch. This will look at cholesterol, electrolyte levels and inflammatory markers. The samples will only be used for this project and any left over at the end of the project will be destroyed.

Testing session 2:
(Location: **FSH or RPH***; Expected Duration:* 1.52 **hours)**
With this session we will ask you to fast for 6 hours before coming in for testing and to abstain from vigorous exercise, caffeine and alcohol for 24 hours before the study.

This will involve the following tests:

Blood vessel function - An ultrasound machine will be used to determine the diameter and blood flow of a large artery of the arm. After images are taken, a blood pressure cuff will be put on your forearm and pumped up for 5 minutes. This may feel slightly uncomfortable and you may experience numbness in your hand and fingers, however this should quickly resolve when the cuff is deflated.

After this we will use the ultrasound machine again to look at how the artery in your arm responds to a dose of a medicine called glyceryl trinitrate. This is commonly used to treat angina and it increases blood flow through the arteries. This drug can sometimes give people a headache and make them feel dizzy. We will take your blood pressure before this and not administer the drug if it is too low to try and avoid any dizziness. Should a headache occur it can be treated with Panadol.

The ultrasound machine will also be used to look at the thickness of an artery in your neck.

Physical activity levels- during this session we will fit you with a small monitoring device that you clip to your body which will measure your physical activity for 1 week.

During this session we will give you a practice go of the computer test looking at your memory and reaction speed that you will do in testing session 3, so that you know what to expect.

Testing session 3:
(Location: **UWA***; Expected Duration:* **2 hours)**
With this session we will ask you to fast for 6 hours before coming in for testing and to abstain from vigorous exercise, caffeine and alcohol for 24 hours before the study.

This will involve the following tests:

Brain blood flow - A special type of ultrasound machine will be used to look at some arteries going to the brain to determine the rate of blood flow to the brain. The probes from this ultrasound machine will be mounted on a head frame, and will sit above and in front of the ears. We will take some measurements with you resting and then we will get you to look at a computer screen. The screen will show a chessboard that changes colours for periods of time. We do this so we can see what happens to the blood flow to a part of the brain. We will also ask you to sit down and stand up several times. This is so we can see how well the brain copes with changes in blood pressure.

Memory and reaction speed - we will ask you to take part in a computer test where you click the right and left buttons on the mouse in response to what the computer program tells you.

Mood questionnaire - Before the memory and reaction speed tests, we will ask you to fill out a questionnaire about your mood by circling boxes on a form. This asks questions about your feelings and emotions over the preceding week. *If the researcher administering the questionnaires identifies that your mental health is being significantly impacted by your heart condition, we will advise you and offer you a referral to a Psychiatrist or Clinical Psychologist for follow up.*

Systemic haemodynamics - blood pressure, heart rate and cardiac output will be measured using a technique that involves placing a small blood pressure cuff around a finger. This finger may feel slightly numb and change colour while the cuff is on, but resolves once the cuff is deflated.

Body composition DEXA scan- we will do a very low dose x-ray scan to look at your body composition. This will involve lying still in a scanner for approximately 10-15minutes. The radiation dose during this scan is very low and is similar to the amount of natural background radiation you would receive during an interstate flight.

Possible side effects and risks

The risk of an adverse event with exercise testing and training is low and regular physical activity and exercise are recommended to maintain good health. The incidence of major complications occurring with exercise testing has been found to be less than 1 per 10000 tests. Rigorous screening will be undertaken prior to any exercise *and you will be carefully monitored by appropriately trained staff at all times to ensure your safety*. Staff supervising exercise sessions will be trained in first aid and a protocol will be in place for any medical emergencies. There is also a risk you may experience some delayed onset muscle soreness after exercise testing, however this should resolve within 48-72 hours.

Possible benefits

Participation in this study will provide you with a supervised exercise program designed to improve your strength and fitness. In addition, the results of the study may help with better management of CHD in the future.

Privacy and Confidentiality

The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with the Privacy Act 1988. Your research data will initially be identified only by a unique study code and held separately from a link that matches the code to your name. No identifiable data (e.g., with your name attached) will leave FSH. Once the study is completed, the data will be anonymised, by deleting the link that matches the code to your name. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

What if something goes wrong?

In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Fiona Stanley Hospital.

Appendix F Recruitment and advertising

F.17 Invitation letter

Government of Western Australia
Department of Health

<Date>

<Patient address>

Dear <Patient title and surname>,

We would like to invite you to take part in a research study looking at the effects of water-based and gym-based exercise in people with coronary heart disease (CHD). **You have been sent this letter because you have received treatment for coronary heart disease at Fiona Stanley Hospital or Royal Perth Hospital.**

Regular exercise has been found to improve the health of people with CHD and reduce the chance of experiencing further heart problems. However, many people with CHD don't undertake enough exercise to receive these benefits. One of the reasons for this may be that the type of exercise recommended to people with heart conditions doesn't suit them. **This research project will investigate if water-based exercise is as effective as gym-based exercise for people with CHD.**

Enclosed is a **Participant Information Sheet & Consent Form** that describes the project in detail and outlines what will be involved should you decide to participate. If you are interested in taking part, or would like to find out more about the project, please:

- Call **(08)** [redacted] to speak to one of the researchers about the project, or,
- Complete and return in the self-addressed envelope the slip below to express an interest in the study. One of the researchers will call you at a time that suits you to discuss the project further.

Kind regards,

[redacted]

A/Prof Andrew Maiorana
Senior Exercise Physiologist
Fiona Stanley Hospital

I _____(print name)

Of

_____

_____(print address)

would like to take part in the water-based exercise for people with coronary heart disease research **or would like to be contacted with further information about the study.**

The best phone number to contact me on is: _____

The best day and time to call me is: _____

F.18 Email for groups

Dear <name>,

We are researchers from Curtin University, Fiona Stanley Hospital and Royal Perth Hospital conducting a study looking at the effects of pool-based exercise training in people with coronary heart disease (Royal Perth Hospital Human Research Ethics Committee REG 15-165).

We are currently recruiting for participants and were wondering if you would be able to put a notice on your website or newsletter to let people know about the study?

We are looking for people aged between 18-80 who have stable coronary heart disease (people who have had a heart attack, stent, or bypass graft surgery at least 6 months ago) and aren't already in a supervised exercise program. Participants will be randomly allocated to 12 weeks of either supervised pool, or gym based exercise training at Fiona Stanley Hospital, or continuing their usual activities. If people would like further information they can contact Anna on [redacted] or [redacted]

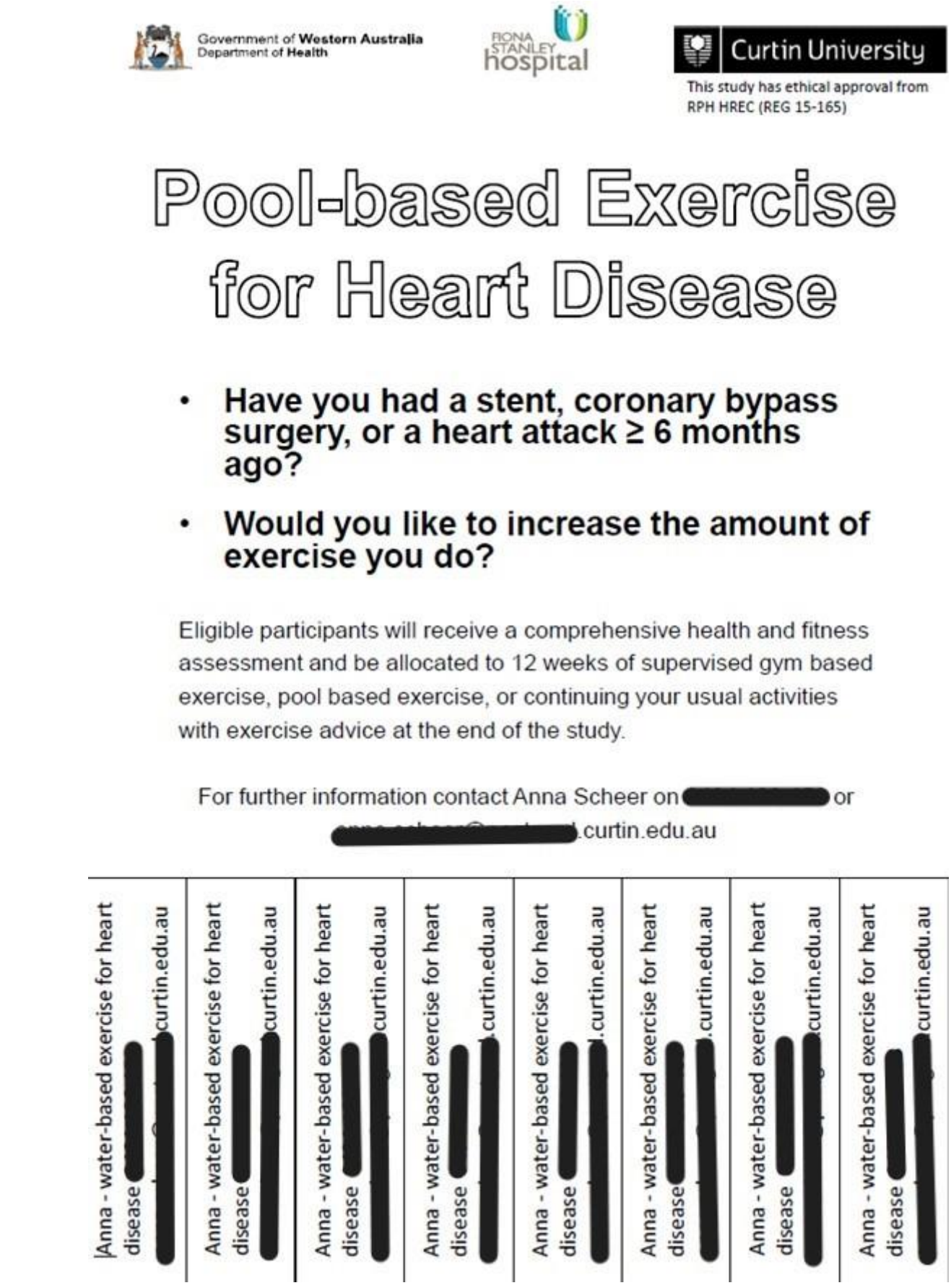
If you have any questions or need any further information please let me know.

Kind regards,

Anna Scheer

PhD Candidate, Curtin University

F.19 Flyer example



F.20 Newspaper advertising

This was displayed in local and state newspapers.

F.21 Radio advertising example

Below is the script approved from the Human Research Ethics Committee. This was run on CurtinFM radio station.

Radio advertisement plan:

Have you had a heart attack, stent or coronary bypass surgery in the past? Are you looking to get more active to improve your health?

Researchers at Curtin University and Fiona Stanley Hospital are investigating whether pool-based exercise training improves fitness and cardiovascular health.

People who take part will undergo a comprehensive health and fitness assessment and will be randomly allocated to supervised gym-based exercise, pool-based exercise, or be asked to maintain their usual activity for a period of 12 weeks. People in the usual activity group will be provided with an individualised exercise program at the end of the study.

For more information please contact Anna Scheer on 04XX XXX XXX or email: XXXXXX

Appendix G Questionnaires

G.22 Screening questionnaire

Screening Survey – Coronary Heart Disease and Exercise Study

Full name		**Date of birth**	
Residential address			
Postal address (if different form above)			
Email			
Contact telephone			
GP contact details			
Cardiologist contact details			

Question: Please mark yes or no or write a response in the space as indicated	**YES**	**NO**
1. Have you been diagnosed by a doctor as having coronary heart disease (or ischaemic heart disease or coronary artery disease)?		
2. How long ago (in years) were you first diagnosed?		
3. Have you ever had a heart attack (myocardial infarction)?		
4. If you answered yes to Q3, have you had more than one heart attack?		
5. If you answered yes to Q3 or Q4, how long ago was/were the heart attack/s?		
6. Have you ever had surgery for your heart or blood vessels?		
7. If you answered yes to Q6 please describe the surgery and roughly when you had it.		

8. Do you have arthritis?		
9. If you answered yes to Q8. please describe the location and severity		
10. Do you have back pain?		
11. Do you have any other pain problems?		
12. If you answered yes to Q10 or 11 please describe the location/ severity of the pain and if it stops you from doing anything.		
13. Are you a current smoker or have you recently quit smoking (in the last 6 months)?		
14. Are you a premenopausal female?		
15. Do you have any problems with your liver?		
16. Do you have any problems with your kidneys?		
17. Do you have any problems with your blood pressure?		
18. Do you have diabetes?		
19. If you answered yes to Q15, 16, 17 or 18 please indicate your current diagnosis and treatment/s.		
20. Have you had any surgery in the last 6 months, or any surgery planned in the coming months?		
21. Have you taken part in an exercise program in the **last 3 months**?		

22. If you answered yes to Q21 please explain how many days per week, for how long each session and what type of exercise it was.		
23. Do you have any history of cancer?		
24. Do you have any conditions that may prevent you from exercising?		
25. Are you available to complete 12 weeks of training 3 times per week if you should be allocated to the training group?		

The following questions are relating to conditions that we need to screen before a participant can enter the pool. Please tick yes or no to the following conditions:

Condition	**Yes**	**No**
Unreliable faecal incontinence		
Severe urinary incontinence		
Active tuberculosis		
Active viral infection		
HIV/AIDS/Hepatitis B		
Shingles (Herpes zoster)		
Cold sores (Herpes simplex)		
Exfoliative or vesicular skin infections (e.g. ringworm, scabies)		
Infected skin rash		
Untreated tinea or plantar warts		
Dermatitis or psoriasis		
Chlorine allergy		
Heat sensitive conditions (e.g. multiple sclerosis, lymphoedema, chronic fatigue)		
Altered sensation in feet/ legs		
Fear of water		

G.23 Medication list

Medications:

Please fill out the following medication table, there is an example at the top to guide you.

Name	Dose	When you take it
e.g. Lipitor (Atorvastatin)	10mg	Evening

Participants filled this out at baseline and follow up assessments.

G.24 Food diary

Food Diary.

For 3 normal days prior to coming in for your testing please write down everything you eat and drink in this food diary. We need this information to check that what you are eating during the study is similar from the beginning to the end. Please try to provide as much information about the food as possible, including brand name. Some examples are shown at the start for you, food from one meal can go in multiple boxes if needed.

Date & time	What
e.g. 27/7/15 9:00am	1 medium sized banana, 1 large choc-chip muffin, 1 cup of Kellogg's cornflakes with skim milk

Participants filled this out prior to baseline and follow up assessments.

Appendix H Case report forms

H.25 Aerobic capacity and body composition

Testing session one- strength and fitness	Participant number _____ Date_____ Tester_____

	Pre arrival:						
	Room & supervision booking confirmed		Cart calibrated				
	Equipment: Tape measure, Goniometer, Pt stickers, masks and ECG dots, sandpaper tape, stopwatch, participants file						
	Pathology form		Pharmacy script for GTN				
	Arrival:						
	Explain session						
	Consent form signed & witnessed						
	Fasted for 4 hours (no food or drink bar water)?						
	Any medication or supplements taken today? YES/NO Name: Time: Usually taken?						
	Any medication usually taken today, but not taken? YES/NO Name: Time usually taken:						
	Collect forms:		Food diary		Medication list		Physical activity
	Provided with pathology and pharmacy forms. Give instructions to do blood test at the hospital, that it is a fasting test (but can have water).						
	Measurements						
	VO_{2peak} test						
	Strength test						
	Confirm vascular testing session time and date. Provide with reminder that this test is fasting, no caffeine or alcohol, medications as per normal, no moderate or vigorous intensity exercise for 24 hrs before.						

Anthropometry			
Height (cm) Shoes off		**Weight (Kg)** Shoes off	

Protocol for waist and hip circumference measurements :
Standing upright, arms relaxed at the side, feet evenly spread apart and body weight even.

Waist circumference widest point of waist

Hip circumference at a level parallel to the floor, at the largest circumference of the buttocks.

Trial:	**1**	**2**	**3**	**Median**
Waist Circ (cm)				
Hip girth (cm)				

Participant number _____
Date_____ Tester_____

VO_{2peak}

Resting measures (after 5min sitting)	HR		BP			
Exercise duration	Minutes		Seconds		Stage reached	
Mask size		Strap size				
Protocol used						
Reason for stopping & peak RPE						
Other symptoms?						
Other comments						

Stage	BP	RPE		Stage	BP
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

H.26 Muscular strength- 1 repetition maximum

Participant number _____
Date_____ Tester_____

1RM Testing Instructions

- **Set 1:** Complete the first set of each exercise at a low intensity, performing 6-8 repetitions of each exercise at an estimated 50% 1RM. Record a RPE value.
- Allow **1 min rest**
- **Set 2:** Adjust weight accordingly, have participant lift and attain another RPE value.
- Allow **1min rest**
- **Set 3:** Adjust weight accordingly, have participant lift and attain another RPE value.
- Allow **2min rest**
- **Set 4 & 5:** repeat as above, **2 min rest** between
- **Allow 2 min rest before next exercise**

Technique and settings guide:

Biceps curl (dominant)		
Technique: • Upper arm supported on bench	**Criteria for successful lift:** • Full range flexion	**Settings:** • Bench height_____ • Arm used **R / L**
Dual leg press extension		
Technique: • Feet shoulder width apart • Hold onto support bars (Do not place hands on knees) • Back against seat • Start position = 90° bend at knee • Extend legs to just before knee lock-out • Controlled return of weight to stack	**Criteria for successful lift:** • Full extension (just before knee lock-out)	**Settings:** • Distance from top of toes to top of push plate: • Seat position: • Back position:
Lat pull down		
Technique: • Knees at 90° • Lower cushion onto top of knees • Straight back • Wide overhand grip • Pull bar down to chin	**Criteria for successful lift:** • Top of bar to bottom of chin	**Settings:** • Distance from pinky finger to end of bar: RHS: _____cm LHS: _____cm
Hamstring curl		
• Knees in line with machine pivot • Back against seat • Hold onto handles but do not brace • Heels just beyond lower pad	**Criteria for successful lift:** • ROM to 90° stopper	**Settings:** • Stopper: • Seat back: • Legs: • Circle:

Participant number _____
Date_____ Tester_____

Exercise	Set 1		1 min	Set 2		1 min	Set 3		2 min	Set 4		2 min	Set 5		2 min
	Wt/rep	RPE		Wt/ reps	RPE		Wt/ reps	RPE		Wt/ reps	RPE		Wt/ Reps	RPE	
Dual Leg Press Extension	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
Biceps curl	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
Lat Pulldown	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
Hamstring curl	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		
	___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps			___kg ___reps		

H.27 Vascular function

Testing session 2- Vascular

Participant number:_____

Date:_____

	Pre arrival:	
	Room and equipment booking confirmed? Checked bed has linen?	
	Equipment: Terason, BP cuff, Dynamap stopwatch, hard drive	
	Arrival:	
	Take to collect GTN and Toilet break (if needed)	
	Explain session- looking at how your blood vessels function- one way to do this is inflating a blood pressure cuff to reduce blood flow into your forearm for 5 min. This will probably make your hand and arm feel numb or tingly. This will go away at the end of the 5 minutes. If you need the cuff down at any time please tell us. The other test involves a spray of glyceryl trinitrate under the tongue. This is an angina medication and makes all of the arteries dilate. This gives some people a headache, but it tends to resolve quickly and you can take some Panadol if required. It can also cause your blood pressure to drop, but we will monitor your blood pressure beforehand and will not give it to you if your blood pressure is low.	
	Any Hx migraines? YES/NO **if yes no GTN**	
	Fasted for 6 hours (no food or drink bar water?)	
	No caffeine containing food or beverages in the last 6 hours?	
	No moderate to vigorous physical activity/ exercise in last 24hrs? No alcohol last 24hrs?	
	Any medication taken today? YES/NO Name: Time: Usually taken?:	
	Any blood pressure lowering or Viagra-type medications taken? YES/NO	
	Any medication usually taken today, but not taken? YES/NO Name: Time usually taken: Taken for:	
	Supine rest 20min	
	BP @ 0min:	
	BP @ 5min:	
	BP@ 10min:	
	BP@ 15min:	
	BP @ 20min:	

Participant number:_____

Date:_____

	Brachial FMD
	Carotid IMT (R and L):
	Rested 20 min since FMD cuff down?
	BP pre GTN: **If SBP <90mmHg or >15mmHg drop from first BP DON'T ADMINISTER**
	GTN test
	Headache? Severity (?/10):
	BP post GTN:
	Final BP & headache rating:
	Offer food/ drink

H.28 Cerebrovascular function and DXA

Testing session 3- CBF/DEXA

Participant number:_____

Date:_____ Tester:_____

	Prior to participant: Turn on gas analyser 20min prior Equipment: TCD, Finapress, Omron, interval app, ECG and dots, Filter, mouthpiece, computers Barometric pressure is:_____ Calibrate gas: Room air O_2%: 20.9476 CO_2%: 0.0314.
	Toilet break (if needed), parking pass
	Explain session-
	Fasted for 6 hours (no food or drink bar water?)
	No caffeine containing food or beverages in the last 6 hours?
	No moderate to vigorous physical activity in the last 24 hours? No alcohol last 24hrs?
	Any medication taken today? YES/NO Name: Time: Usually taken?:
	Any medication usually taken today, but not taken? YES/NO Name: Time usually taken: Taken for:
	TCD set up, photo taken of R and L sides, screen output
	Finapress and brach cal Finapress arm: L / R Resting baseline 5min- instructions to stay as still as possible and breathe through the mouthpiece. BP x 3 (Omron) 1. 2. 3. Ave:
	Neurovascular coupling Table height from ground _____cm Monitor to nose _____cm Monitor screen used: Notes:

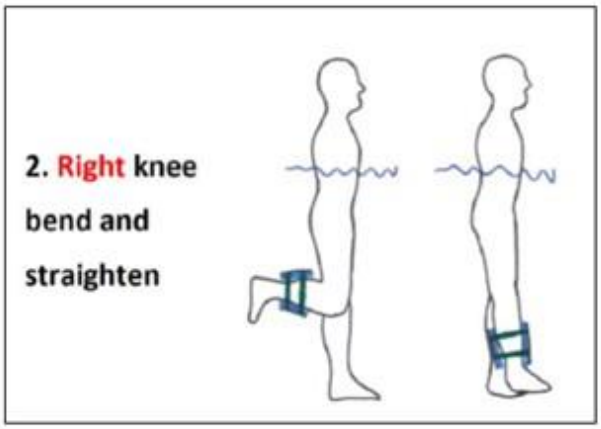
Participant number:_____

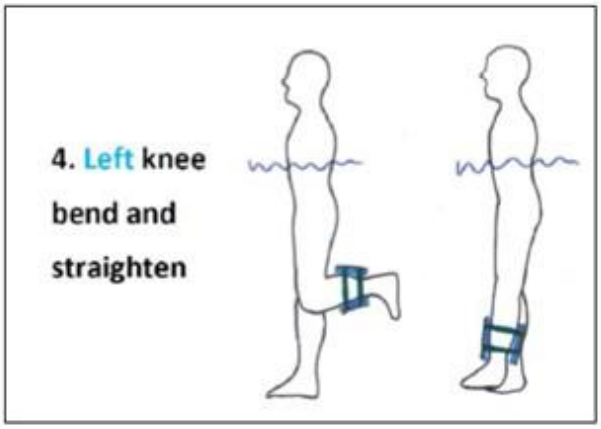
Date:_____ Tester:_____

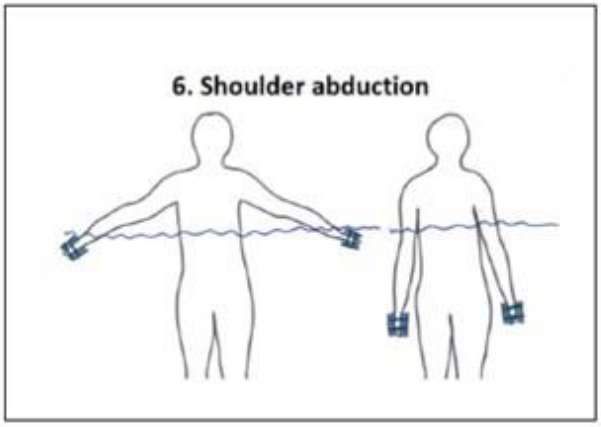
	Dynamic cerebral autoregulation- (3min) 3s BP pre: Standing BL (mouthpiece in) (1min) Standing BP: Squat stands 3min of 3s
	2-3 min rest (sitting)
	Dynamic cerebral autoregulation-(3min) 6s Sitting BP pre: Standing BL (mouthpiece in) (1min) Standing BP: Squat stands 3min of 6s
	DEXA – Metal removed (belt, zip, underwire) Notes:

Appendix I Exercise programs

I.29 Pool program participant exercises



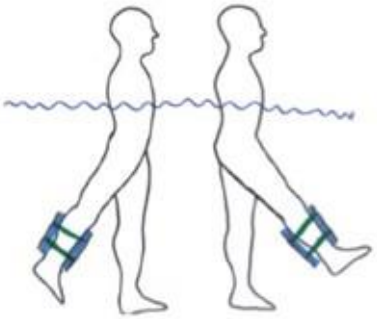




7. Walk / Jog

Jogging on the spot or across the pool to your target heart rate. Turning and moving back through your turbulence will make it harder

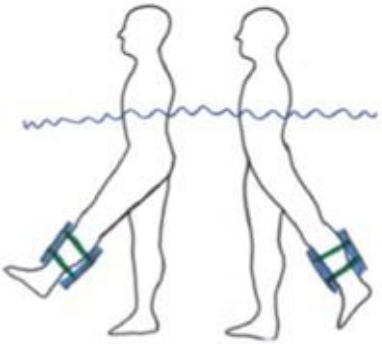
8. Right hip forwards and back



9. High knees

Bring your knees up towards your chest and down. You can pump your arms up and down too.

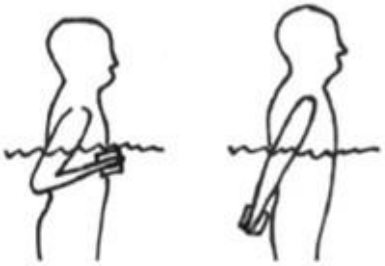
10. Left hip forwards and back

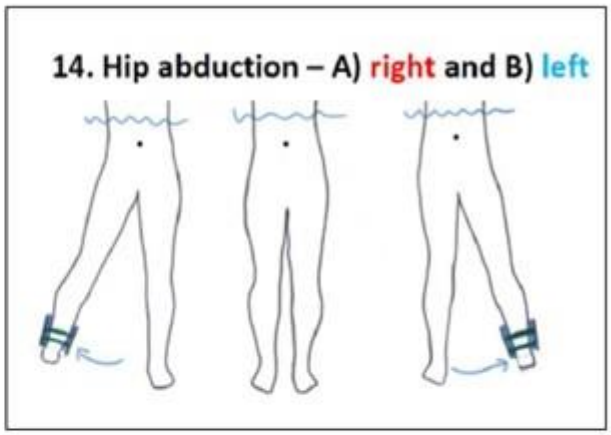


11. Walk / Jog

Jogging on the spot or across the pool to your target heart rate. Turning and moving back through your turbulence will make it harder

12. Biceps and triceps

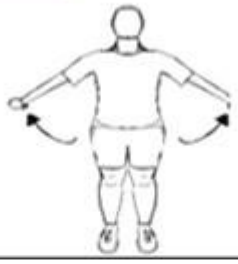




These were printed as an A4 landscape booklet (1 exercise per page) and laminated to allow them to be seen from a distance by participants. Settings could be recorded on stickers and updated as required.

I.30 Gym program participant exercises

1.Treadmill	9.Treadmill
2.Knee Extension 	10A. Left hip forwards 
3.Bike	11.Bike
4.Hamstrings 	12A. Biceps 
5.Treadmill	13.Treadmill
6A.Lat pulldowns 	14A. Right hip abduction 
7.Bike	15.Bike
8A. Right hip forwards 	

1.Treadmill	9.Treadmill
2.Knee Extension 	10B. Left hip backwards 
3.Bike	11.Bike
4.Hamstrings 	12B. Triceps 
5.Treadmill	13.Treadmill
6B.Shoulder flapping 	14B. Left hip abduction 
7.Bike	15.Bike
8B. Right hip backwards 	

Each page represents 1 circuit (A and B), these were printed in half size, laminated on a lanyard and had settings/ weights for each exercise on stickers updated when participants progressed as a prompt for participants.

I.31 Pool program recording sheet

Participant_____ Week_____

Exercise	Session 1 BP pre:		BP post:		Session 2 BP pre:		BP post:		Session 3 BP pre:		BP post:	
	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE
1. Hi Knee	↑knee				↑knee				↑knee			
2. R KE/F	R KE/F				R KE/F				R KE/F			
3. Jog	Jog				Jog				Jog			
4. L KE/F	L KE/F				L KE/F				L KE/F			
5. Hi knee	↑knee				↑knee				↑knee			
6. sh abd	sh abd				sh abd				sh abd			
7. Jog	Jog				Jog				Jog			
8. R HF/E	R HF/E				R HF/E				R HF/E			
9. Hi Knee	↑knee				↑knee				↑knee			
10. L HF/E	L HF/E				L HF/E				L HF/E			
11. Jog	Jog				Jog				Jog			
12. Bi/tric	B/T				B/T				B/T			
13. Hi Kne	↑knee				↑knee				↑knee			
14a. R Hab	Rab				Rab				Rab			
14b. L Hab	Lab				Lab				Lab			
15. Jog	Jog				Jog				Jog			

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

I.32 Gym program recording sheet

Participant_____ Week_____

Exercise	Session 1 BP pre:		BP post:		Session 2 BP pre:		BP post:		Session 3 BP pre:		BP post:	
	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE	Setting	R1 HR/RPE	R2 HR/RPE	R3 HR/RPE
1. Trdml	T				T				T			
2. KE	KE				KE				KE			
3. Cyc	Cy				Cy				Cy			
4. HS	HS				HS				HS			
5. Trdml	T				T				T			
6a. lats	Lat				Lat				Lat			
6b. sh abd	Abd				Abd				Abd			
7. cycling	Cy				Cy				Cy			
8a. R HF	rHF				rHF				rHF			
8b. R HE	rHE				rHE				rHE			
9. trdml	T				T				T			
10a. L HF	LHF				LHF				LHF			
10b. L HE	LHE				LHE				LHE			
11. cyc	Cy				Cy				Cy			
12a. Bicep	Bi				Bi				Bi			
12b. Tricp	Tri				Tri				Tri			
13. Trdml	T				T				T			
14a. R Hab	RAb				RAb				RAb			
14b. L Hab	LAb				LAb				LAb			
15. Cyc	Cy				Cy				Cy			

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

☐ No chest pain/ discomfort
☐ No new injuries/illnesses
☐ All normal meds taken

Appendix J Permission statements for publications

J.33 Chapter 3

This article was published as open access in the Journal of Physiotherapy, which allows the article to be article to be shared, in unaltered form, with appropriate attribution under a Creative Commons License: CC BY-NC-ND 4.0 DEED.

The article can be found:

Scheer A, Shah A, Ito Ramos de Oliveira B, Moreno-Suarez I, Jacques A, Green D, and Maiorana A. Twelve weeks of water-based circuit training exercise improves fitness, body fat and leg strength in people with stable coronary heart disease: a randomised trial. Journal of Physiotherapy 67: 284-290, 2021.https://doi.org/10.1016/j.jphys.2021.08.012

J.34 Chapter 4

Information on the American Physiological Society (APS) copyright policy can be found: https://journals.physiology.org/publication-process#copyright

REUSE OF APS CONTENT BY APS AUTHORS

Authors of APS articles may reuse their content in the following situations:

Type of Use	Allowed?	Terms*
Reuse in New Works	**Yes**	Full citation is required.
Meeting Presentations and Conferences	**Yes**	A copyright fee will apply if there is a charge to the user or if the meeting is commercially supported. Full citation is required.
Theses and Dissertations	**Yes**	Whole articles may be reproduced in dissertations and posted to thesis repositories. Full citation is required.

The article can be found:

Scheer A, Ito Ramos De Oliveira B, Shah A, Jacques A, Chasland LC, Green DJ, and Maiorana AJ. The effects of water-based circuit exercise training on vascular function in people with coronary heart disease. American Journal of Physiology-Heart and Circulatory Physiology 325: H1386-H1393, 2023. https://doi.org/10.1152/ajpheart.00468.2023