School of Physiotherapy and Exercise Science

Exploring Approaches to Exercise Testing and Training in Adults with Cystic Fibrosis

Abbey Sawyer

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

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in a university.

Abbey Sawyer

ORCID: 0001-5153-5927

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STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy (Exercise, Sport & Rehabilitation [DREXSPRH]) at Curtin University in Perth, Western Australia. Studies were undertaken between October 2016 and May 2020, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Department of Pulmonary Physiology, the Respiratory Medicine Department and the Physiotherapy Department at Sir Charles Gairdner Hospital, as well as the Institute for Respiratory Health, Western Australia.

This program of research was developed in association with my supervisors, who have been involved in editing both the thesis and all associated publications.

All material presented in this thesis is original.

ABSTRACT

Overview

This program of research included four studies, and the current PhD thesis comprises eight chapters. The overall aim of this program of research aimed to explore approaches to exercise testing and training in adults with chronic respiratory conditions, in particular, cystic fibrosis (CF). Chapters 1 provides the Introduction to the program of research. Chapter 2 presents the Literature Review. Within the Literature Review, a **narrative review and meta-analysis** was undertaken to explore the effects of high intensity interval training (HIIT) on exercise capacity in people with chronic respiratory conditions. Where there was a dearth of literature in the CF population, data collected in other chronic respiratory conditions were reviewed. Chapter 3 was a **survey** undertaken to report the exercise testing and exercise training procedures in CF centres in Australia and New Zealand. Chapters 4 to 6 was a **randomised controlled trial** (RCT) undertaken to evaluate the effects of HIIT on exercise capacity, health-related quality of life (HRQoL), exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. The methods of this RCT have been published in a peer-reviewed journal and are available in Chapter 4. Baseline data collected as part of the RCT were used to compare the physiological and symptom responses of people with CF to two different **laboratory-based exercise tests**. The findings of this comparison are presented in Chapter 5, and the **main results** and discussion of the **RCT** are presented in Chapter 6. Chapter 7 (Part 1) presents a **systematic review** conducted to classify interventions aimed at optimising participation in physical activity as 'promising' or 'not promising' in people aged 15 to 45 years with chronic cardiorespiratory conditions, and categorise the behaviour change techniques (BCTs) within these interventions. Finally, the mapping of the **BCTs** employed within the RCT conducted as part of this research program are reported in Chapter 7 (Part 2).

Narrative review and meta-analysis (Chapter 2, Part 5)

Background and research question

Exercise training is important in the management of people with chronic cardiorespiratory conditions. However, it can be difficult for these people to achieve or maintain exercise training intensities sufficient to elicit physiological adaptation. Interval-based training, in particular HIIT, may be used as a strategy to optimise the load that can be tolerated during

exercise training. A solicited review was conducted to answer the following research question: what is the evidence around land-based whole-body HIIT on exercise capacity in adults living with chronic respiratory conditions, including people with chronic obstructive pulmonary disease (COPD), CF, non-CF bronchiectasis, asthma, interstitial lung diseases and non-small cell lung cancer?

Methods

The literature was reviewed (six databases) from inception to July 2019 (from 2010 to July 2019 for COPD). Studies undertaken in adults with a chronic respiratory condition were included if participants were randomised to receive: (i) HIIT or no exercise, or (ii) HIIT or moderate intensity continuous exercise. To evaluate the training effect, data were extracted on the peak rate of oxygen uptake (VO_{2peak}) and/or peak work rate (W_{peak}). Meta-analyses were conducted where possible.

Results

In people with COPD, two studies demonstrated between-group differences favouring HIIT compared with no exercise, showing a mean difference (MD) [95% confidence interval (CI)] for VO_{2peak} of 4 $mL \cdot kg^{-1} \cdot min^{-1}$ [1 to 7], and for W_{peak} of 16 Watts (W) [5 to 27]. However, meta-analyses demonstrated no advantage of HIIT compared with continuous exercise on these outcomes: VO_{2peak} MD [95% CI] −0.13 $L \cdot min^{-1}$ [−0.05 to 0.03], eight studies; and W_{peak} MD [95% CI] 0.73 W [−3.84 to 5.21], nine studies. In people with CF, no study compared HIIT to no exercise, and the two studies that compared HIIT to continuous exercise reported similar benefits for both training types. In people with non-small cell lung cancer, prior to resection, one study demonstrated a between-group difference in favour of HIIT compared with no exercise for VO_{2peak} (MD [95% CI] 4 $mL \cdot kg^{-1} \cdot min^{-1}$ [2 to 6]). In people with asthma, one study demonstrated a between-group difference in favour of HIIT compared with no exercise for VO_{2peak} (MD ± standard deviation 3 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$) and one that compared HIIT to continuous exercise reported similar benefits for both training types. No studies were identified in people with non-CF bronchiectasis or interstitial lung diseases.

Conclusions

In people with COPD, HIIT increases exercise capacity when compared with no exercise. There appears to be no clear benefit in exercise capacity for HIIT compared to continuous exercise. There is a paucity of studies exploring the effects of HIIT in people with other respiratory conditions, and in particular, there is little evidence to support the use of this type of exercise training in people with CF.

Survey (Chapter 3)

Background and research question

Current national and international recommendations support the provision of annual exercise testing, as well as education and support for regular exercise training, in people with CF. To date, there are no data pertaining to these factors within Australian and New Zealand CF centres. This study sought to answer the following research question: what is the extent and scope of, and importance placed on, exercise testing and exercise training in Australian and New Zealand CF centres? Specifically, we sought to explore differences in: (i) the utility of annual exercise testing; (ii) the nadir peripheral capillary oxygen saturation (i.e. cut-off value; SpO_2), below which testing and training would be terminated (or rests imposed); and (iii) the proportion of CF centres who provide an exercise training program.

Methods

A survey was developed to collect information pertaining to the extent and scope of, and importance placed on, exercise testing and exercise training within Australian and New Zealand CF centres. The online survey comprised five sections (demographics, laboratory-based exercise testing, field-based exercise testing, strength testing and exercise training) consisting of 46 questions. The survey was circulated to a member of each centre's CF team for completion over a 3-month period, and the response rate was optimised using the Dillman approach.

Results

A response rate of 80% (32/40) was achieved. Each state/territory in Australia, except the Northern Territory, was represented by at least one site. Eight of the 12 major regions in New Zealand were represented by at least one site. Regarding tests of exercise capacity, CF centres performed field tests more commonly than laboratory tests (28/32 [88%] versus 11/32 [34%]; difference: 54%; 95% CI 31% to 70%). Most (88%) respondents perceived field tests to be at least 'somewhat' important, whereas 90% of respondents perceived laboratory tests to be 'a little' to 'somewhat' important. Regarding exercise training, the importance of regular participation in physical activity and/or exercise was discussed by at least one health professional in the CF team at every clinic appointment and/or annual review. Some form of outpatient exercise training program was offered to patients in most centres (24/32; 75%).

Discussion and conclusion

This survey describes the current exercise testing and training practices, and the importance placed upon these practices, in Australian and New Zealand CF centres. The main findings of this survey were: (i) the majority of CF centres do not undertake laboratory-based exercise tests and, if performed, these tests are generally undertaken on the minority of patients and/or for non-clinical (i.e. research) purposes; (ii) almost all CF centres undertake field-based exercise testing on at least half of their patients annually; (iii) exercise training is discussed by at least one health professional in the CF team at every clinic appointment and/or at annual review; and (iv) most centres offer some form of exercise training program to patients. However, this is generally prioritised for patients with more severe respiratory disease and those awaiting lung transplantation. The response rate for the survey was 80% and, therefore, the results are representative of current practices in exercise testing and training within CF centres across Australia and New Zealand.

Comparison of exercise testing responses (Chapter 5)

Background and research questions

Maximal incremental ramp-based cycle ergometry tests are generally seen as a 'gold-standard' method of assessing exercise capacity in people with chronic respiratory conditions, including CF. Earlier work suggests that measures of submaximal exercise capacity (i.e. endurance) are more responsive to change than peak measures of exercise capacity in people with chronic respiratory disease, and may also have prognostic utility.

There is limited literature on the physiological and symptom responses to constant work rate cycle ergometry tests in people with CF. This study sought to answer the following research questions: in adults with CF, (i) how do the physiological and symptom responses during a constant work rate cycle ergometry test compare to those elicited during a maximal incremental ramp-based cycle ergometry test; and (ii) what are the limits of agreement of peak measures during the two cycle ergometry tests?

Methods

This study forms part of the baseline results for the RCT conducted as part of the PhD program of research. People with CF were asked to attend two assessment sessions on non-consecutive weekdays lasting approximately 1½ hours each. Measures of exercise capacity were recorded using a ramp-based cycle ergometry test (first assessment session) and a constant work rate cycle ergometry test (second assessment session) at 80% of the peak work rate of the ramp-based test. Both tests comprised 1 minute of 'rest', 1 minute of unloaded cycling, a 'work' phase and a 5-minute 'recovery'.

Results

In 14 participants (43% female, median [interquartile range; IQR] aged 31 [28, 35] years, forced expiratory volume in 1 second [FEV_1] 61 [45, 80] % predicted), there were no differences in the physiological responses between the two tests. The duration was shorter in the constant work rate cycle ergometry test (between-group MD [95% CI] 285 s [201 to 369]). Leg muscle fatigue was the predominant symptom at the end of the test (79% and 72% for the ramp-based and constant work rate cycle ergometry test, respectively).

Discussion and conclusion

In adults with CF, this is the first study to demonstrate trivial differences in the end-test exercise responses between a ramp-based and constant work rate cycle ergometry test. Although the constant work rate test was shorter in duration, it elicited similar peak responses as the ramp-based test. The results of this study provide evidence that the constant work rate cycle ergometry test, when conducted at 80% of the W_{peak}, elicits peak physiological and symptom responses.

Randomised controlled trial (Chapter 6)

Background and research questions

Despite the benefits of exercise training in people with CF, the recommendation to complete 30 to 60 minutes of aerobic exercise daily at a moderate intensity may not be possible. Consistent with the general population, people with CF have competing demands on their time for work, study and family, but they also have a high daily treatment burden. In addition, little participation in exercise may be a mechanism to minimise the onset of intolerable symptoms of dyspnoea and muscle fatigue associated with exercise. An alternative training approach such as HIIT may be a more time-efficient and tolerable option to optimise exercise capacity. The specific research question answered in this chapter was: in people with CF, what was the effect of an 8-week low-volume HIIT program, compared with weekly contact and no formal exercise training, on exercise capacity (primary outcome), HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment (secondary outcomes)? Secondary research questions also answered were: in people with CF who were allocated to the experimental group of the RCT, (i) what proportion of participants developed post-exercise quadriceps femoris muscle soreness each week during the 8-week HIIT program, and how severe was this symptom; (ii) how well did the participants tolerate the HIIT program; and (iii) what were the participants' reflections on the facilitators and barriers following the HIIT program?

Methods

Participants were asked to undertake a baseline assessment period. They were then randomly allocated using a national randomisation service to a control group that received usual care and weekly contact, or an experimental group that received usual care and thrice-weekly HIIT. The HIIT sessions comprised a 2-minute warm-up, six sets of work (30 seconds each), six sets of rest (30 seconds each), and a 2-minute cool-down on a cycle ergometer with a physiotherapist present. Participants were then asked to undertake a follow-up assessment following the 8-week intervention period. Outcome measures at baseline and follow-up were: exercise capacity (T_{lim} during a constant work rate cycle ergometry test, peak work rate [W_{peak}] and the peak rate of oxygen uptake [VO_{2peak}] during a ramp-based cycle ergometry test); HRQoL (Cystic Fibrosis Questionnaire Revised [CFQ-R] and Alfred Wellness Score for CF); exercise self-efficacy (Barriers Self-Efficacy Scale); feelings of anxiety and depression (Hospital Anxiety and Depression Scale); and exercise enjoyment (Physical Activity Enjoyment Scale). In the experimental group only, tolerance was recorded using attendance and completion data and the incidence of post-exercise muscle soreness. Participants allocated to the experimental group were invited to undertake a semi-structured interview upon completion of the HIIT program ('debrief'). These sessions were audio-recorded to allow for transcription and analysis of common themes.

Results

Fourteen participants (43% female, median [IQR] aged 31 [28, 35] years, FEV_1 61 [45, 80] % predicted) were randomly allocated into the experimental (n = 7) or control groups (n = 7). The magnitude of change in T_{lim} seen during the constant work rate cycle ergometry test in the experimental group was greater than in the control group (between-group difference p = 0.017). The magnitude of change in W_{peak} (W) during the ramp-based cycle ergometry test was also greater in the experimental group than in the control group (between-group difference p = 0.017). This change was also demonstrated when W_{peak} was expressed as a percentage of the predicted value and as a proportion of weight (kg). There were no other between-group differences for the ramp-based cycle ergometry test. The magnitude of change in the physical functioning domain of the CFQ-R was greater in the experimental group than in the control group (between-group difference p = 0.03). There were no other between-group differences in other questionnaire measures.

The median [IQR] percentage of sessions attended by participants in the experimental group was 93% [83, 95]. Of the sessions attended, 100% of the participants were able to complete each session in its entirety. Of the seven participants allocated to the experimental group, five agreed to undertake a debrief interview. The main factors facilitating participation in the HIIT program were: (i) tolerability, (ii) time commitment/flexibility, (iii) exercise enjoyment, and (iv) the presence of a therapist.

Discussion and conclusion

This is the first RCT to evaluate the effects of 8 weeks of low-volume HIIT on exercise capacity, HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. This RCT demonstrated that 8 weeks of low-volume HIIT produced greater magnitude of change in T_{lim} and W_{peak} over and above the magnitude of change by continuing usual care (control group) in people with CF. The improvements in T_{lim} (seconds) and W_{peak} (W) for the experimental group were 101% [43, 72] and 40% [11, 5] of the baseline values, respectively. These are compared to a change of <7% in the control group for both of these measures. Of interest, W_{peak} has been shown to be a predictor of survival or need for lung transplantation at 10-year follow-up. These improvements were demonstrated despite the time commitment of the HIIT program being only 30 minutes per week. The HIIT program was well tolerated and accepted by participants allocated to the experimental group. No between-group changes in other outcome measures were observed.

Systematic review (Chapter 7, Part 1)

Background and research questions

To address issues related to poor participation in physical activity including exercise training, there is growing interest in the use of BCTs. These techniques are the active component(s) of an intervention aimed to modify existing or stimulate new behaviours. The research questions of Part 1 of Chapter 7 were: in published work done in adolescents and adults with one or more chronic cardiorespiratory conditions, (i) which interventions aimed at optimising participation in physical activity appear to be 'promising' or 'not promising'; and (ii) which BCTs could be identified and mapped from the 'promising' and 'not promising' interventions?

Methods

Nine databases and registries were searched (October 2017) for studies that reported objective measures of physical activity before and after an intervention period. Interventions were classified as 'promising' if a between-group difference in physical activity was demonstrated. Michie et al.'s (2013) BCT Taxonomy v1 was used to unpack the BCTs within interventions. The taxonomy includes a total of 93 BCTs.

Results

Six studies (n = 396 participants) were eligible for inclusion in this systematic review. Of these, participants had a diagnosis of CF (n = 2 studies), asthma (n = 2 studies) or congenital heart disease (n = 2 studies). The interventions of three studies were classified as 'promising'. Nineteen (20%) of 93 BCTs were described within the interventions. The most commonly used BCTs comprised goal setting, action planning and social support. Five BCTs were solely used in 'promising' interventions, including problem solving, information about antecedents, information about health consequences, pros and cons, and comparative imagining of future outcomes.

Discussion and conclusion

This systematic review demonstrated that only 20% of BCTs were utilised in the included studies. Despite the growing consensus surrounding the importance of BCTs to change health behaviours, this systematic review has demonstrated that details of specific interventional BCTs may be underreported, or BCTs may not be considered fully when devising an intervention in adolescents and adults with a chronic cardiorespiratory condition.

At present, there is limited evidence to support the use of individual BCTs, or specific combinations of BCTs, over others within interventions aiming to optimise physical activity in adolescents and adults with chronic cardiorespiratory conditions.

Process evaluation (Chapter 7, Part 2)

Research question

The research question of this chapter was: in people with CF who were randomly allocated to the experimental group of the RCT conducted in this research program, which BCTs and psychological processes were organically employed to optimise participation in the HIIT intervention?

Methods

In the seven participants allocated to the experimental group, HIIT sessions were audio-recorded for analysis of BCTs and for fidelity checking. Michie et al.'s (2013) BCT Taxonomy v1 was used to unpack the BCTs within the intervention. The psychological mechanisms of action of the BCTs were explored.

Results

Fifteen of a possible 93 BCTs (16%) were incorporated within the HIIT intervention. Three of these BCTs were mapped on more than one occasion. Of 26 possible mechanisms of action, 12 (46%) were identified in the BCTs incorporated within the intervention of this study. Of these, feedback processes and goals were the most commonly linked psychological mechanisms.

Discussion and conclusion

The mapping of BCTs highlights the numerous diverse components of the HIIT intervention, including the specific tasks often labelled as therapist supervision, designed to facilitate changes in behaviour. Ongoing precise reporting of interventions and consideration of BCTs will allow for more precise and meaningful evidence synthesis in future systematic reviews, and accurate translation of interventions into clinical practice.

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PUBLICATIONS ARISING AS PART OF THESIS

Peer-reviewed journals

Sawyer A, Cavalheri V, Hill K. Effects of high intensity interval training on exercise capacity in people with chronic pulmonary disease: a narrative review. BMC Sports Sci Med Rehabil. 2020;30(12):22. doi:10.1186/s13102-020-00167-y.

Sawyer A, Cavalheri V, Wood J, Hill K. Exercise testing and exercise training within cystic fibrosis centres across Australia and New Zealand: what is considered important and what is current practice? Intern Med J. 2019; [Epub ahead of print]. doi:10.1111/imj.14443.

Sawyer A, Lewthwaite H, Gucciardi D, Hill K, Jenkins S, Cavalheri V. Behaviour change techniques to optimise participation in physical activity or exercise in adolescents and young adults with chronic cardiorespiratory conditions: a systematic review. Intern Med J. 2019;49(10):1209-1220. doi:10.1111/imj.14141.

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Effects of high intensity interval training on exercise capacity in people with cystic fibrosis: study protocol for a randomised controlled trial. BMC Sports Sci Med Rehabil. 2018;6(10):19. doi:10.1186/s13102-018-0108-2.

Under review

Sawyer A, Cavalheri V, Jenkins S, Wood J, Singh B, Hill K. Endurance cycle ergometry tests performed at a sub-maximal work rate elicit peak physiological and symptom responses in adults with cystic fibrosis. Submitted to Respiratory Care, February 2020.

Manuscripts in preparation

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Effects of high intensity interval training on exercise capacity in people with cystic fibrosis: a randomised controlled trial.

ABSTRACTS & PRESENTATIONS

2020:

Poster presentations

Sawyer A, Cavalheri V, Hill K. A review of the effects of high intensity interval-based training on exercise capacity in adults with a chronic respiratory condition: where are we now and what is next? Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2020. *Cancelled due to COVID-19.*

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Low-volume high intensity interval training improves exercise endurance capacity and is well tolerated in people with cystic fibrosis: a randomised controlled trial. American Thoracic Society – Annual Scientific Meeting, 2020. *Cancelled due to COVID-19.*

Oral presentations

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Low-volume high intensity interval training improves exercise endurance capacity and is well tolerated in people with cystic fibrosis: a randomised controlled trial. Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2020. *Cancelled due to COVID-19.*

2019:

Poster presentations

Sawyer A, Cavalheri V, Wood J, Hill K. Exercise testing and training practices in Australian and New Zealand CF centres. Proceedings of Research Week at Sir Charles Gairdner Hospital, 2019. p.1.

Sawyer A, Cavalheri V, Hill K, Jenkins S, Wood W, Cecins N, Singh B, Gucciardi D. "Short and sweet… I really enjoyed it!" Tolerance and experiences of a high intensity interval training program in people with cystic fibrosis. Program Booklet of the Australasian Cystic Fibrosis Conference, 2019 (EP115) and Proceedings of Research Week at Sir Charles Gairdner Hospital, 2019. p.1.

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Adults with cystic fibrosis display similar cardiorespiratory and symptomatic responses during maximal ramp and constant work rate cycle ergometry tests. Program Booklet of the Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2019. p.76 (Abstract Number TP065).

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Heart rate recovery following maximal and submaximal exercise is impaired in adults with cystic fibrosis. Program Booklet of the Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2019. p.76 (Abstract Number TP066).

Oral presentations

Sawyer A, Cavalheri V, Hill K. Effects of high intensity interval training on exercise capacity in chronic respiratory disease: a review. Curtin School of Physiotherapy and Exercise Science Community Thank You Event, 2019 (invited presentation).

Sawyer A, Cavalheri V, Wood J, Hill K. Exercise testing and training practices in Australian and New Zealand CF centres. Australasian Cystic Fibrosis Conference, 2019 (O116).

2018:

Poster presentations

Sawyer A, Lewthwaite H, Gucciardi D, Jenkins S, Hill K, Cavalheri V. Behaviour change techniques to optimise daily physical activity or participation in exercise in adolescents and adults with chronic cardiorespiratory conditions: a systematic review. Program Booklet of the Western Australia branch of the Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2018. p.23.

Sawyer A, Lewthwaite H, Gucciardi D, Jenkins S, Hill K, Cavalheri V. Behaviour change techniques to optimise daily physical activity or participation in exercise in adolescents and adults with chronic cardiorespiratory conditions: a systematic review. Proceedings of Research Week at Sir Charles Gairdner Hospital, 2018. p.1.

Oral presentations

Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Fit in 10 minutes. Proceedings of the 3-Minute Thesis Competition, Curtin University, 2018 (*Finalist*).

Sawyer A, Lewthwaite H, Gucciardi D, Jenkins S, Hill K, Cavalheri V. Behaviour change techniques to optimise daily physical activity or participation in exercise in adolescents and adults with chronic cardiorespiratory conditions: a systematic review. Proceedings of Mark Liveris Student Research Conference, 2018. p.2 (*Awarded 2nd place*).

Sawyer A, Lewthwaite H, Gucciardi D, Jenkins S, Hill K, Cavalheri V. Behaviour change techniques to optimise daily physical activity or participation in exercise in adolescents and adults with chronic cardiorespiratory conditions: a systematic review. Proceedings of Research Week at Sir Charles Gairdner Hospital, 2018. p.1 (*Awarded the Allied Health New Investigator of the Year Award*).

CO-AUTHORSHIP

Abstracts

Gaynor M, **Sawyer A**, Jenkins S, Wood J. Variable agreement between wearable heart rate monitors during exercise in cystic fibrosis. Program Booklet of the Western Australia branch of the Thoracic Society of Australia and New Zealand – Annual Scientific Meeting, 2018. p.23.

Publications

Gaynor M, **Sawyer A**, Jenkins S, Wood J. Variable agreement between wearable heart rate monitors during exercise in cystic fibrosis. ERJ Open Res. 2019;5(4):pi=00006-2019. doi:10.1183/23120541.00006-2019.

AWARDS & GRANTS

Thoracic Society of Australia and New Zealand Annual Scientific Meeting – Travel Award (2020) – *Cancelled due to COVID-19*

Higher Degree by Research Mobility Award (to attend the American Thoracic Society Annual Scientific Meeting in Philadelphia, USA, and the McMaster University in Hamilton, Canada) – Curtin University (2019) – *Cancelled due to COVID-19*

Thoracic Society of Australia and New Zealand Annual Scientific Meeting – Travel Award (2019)

Allied Health New Investigator of the Year Award – Sir Charles Gairdner Hospital (2018)

Mark Liveris Conference (Awarded 2nd place prize for the oral presentation section) – Curtin University (2018)

3 Minute Thesis® Competition (Finalist, oral presentation) – Curtin University (2018)

Research Advisory Committee Grant – Sir Charles Gairdner Hospital (2017/18)

PhD Top-up Scholarship – Australian Cystic Fibrosis Research Trust (2017)

Institute for Respiratory Health – Conquer Cystic Fibrosis Research Scholarship (2016)

PROFESSIONAL SERVICE & LEADERSHIP

Chair of the Western Australian branch of the Australian Physiotherapy Association Cardiorespiratory Group (January 2019 to present)

Social coordinator and member of Western Australian Respiratory Research Physiotherapists (January 2019 to present)

Alumni representative of the External Advisory Board – University of Notre Dame (2016 to present)

Member of the Thoracic Society of Australia and New Zealand (2016 to present)

Member of the European Respiratory Society (2016 to present)

Member of the Institute for Respiratory Health (2015 to present)

LIST OF ABBREVIATIONS

ACBT: Active cycle of breathing technique
AweScore-CF: Alfred Wellness Score for Cystic Fibrosis
BARSE: Barriers Self-Efficacy Scale
BCT: Behaviour change technique
BMI: Body mass index
BP: Blood pressure
bpm: beats per minute
CF: Cystic fibrosis
CFRD: Cystic fibrosis–related diabetes
CFQ-R: Cystic Fibrosis Questionnaire Revised
CFTR: Cystic fibrosis transconductance regulator
CI: Confidence interval
COPD: Chronic obstructive pulmonary disease
CPET: Cardiopulmonary exercise test
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
HADS: Hospital Anxiety and Depression Scale
HIIT: High intensity interval training
HR: Heart rate
$HR_{max/peak}$: Maximal/peak heart rate
HRQoL: Health-related quality of life
IQR: Interquartile range
ISD: Interstitial lung diseases
ISWT: Incremental shuttle walk test
MD: Mean difference
MCID: Minimal clinically important difference
NSCLC: Non-small cell lung cancer
OR: Odds ratio
PACES: Physical Activity Enjoyment Scale
PAH: Pulmonary arterial hypertension
PCH: Perth Children's Hospital
PEP: Positive expiratory pressure
RCT: Randomised controlled trial
SCGH: Sir Charles Gairdner Hospital
SD: Standard deviation
SpO_2: Peripheral capillary oxygen saturation
T_{lim}: Time to symptom limitation
UK: United Kingdom
USA: United States of America
VAS: Visual analogue scale
VCO_2: Carbon dioxide production
VCO_{2peak}: Peak rate of carbon dioxide production
VE: Minute ventilation
VE_{peak}: Peak minute ventilation

VO_2: Oxygen uptake
VO_{2peak}: Peak rate of oxygen uptake
W_{peak}: Peak work rate
6MWD: 6-minute walk distance
6MWT: 6-minute walk test

CHAPTER 1

INTRODUCTION

Overview

This chapter will outline the background and research questions for the studies undertaken as part of this program of research. The overall aim of this program of research aimed to explore approaches to exercise testing and training in adults with chronic respiratory conditions, in particular, cystic fibrosis (CF). Chapters 1 provides the Introduction to the program of research. Chapter 2 presents the Literature Review. Within the Literature Review, a **narrative review and meta-analysis** was undertaken to explore the effects of high intensity interval training (HIIT) on exercise capacity in people with chronic respiratory conditions. Where there was a dearth of literature in the CF population, data collected in other chronic respiratory conditions were reviewed. Chapter 3 was a **survey** undertaken to report the exercise testing and exercise training procedures in CF centres in Australia and New Zealand. Chapters 4 to 6 was a **randomised controlled trial** (RCT) undertaken to evaluate the effects of HIIT on exercise capacity, health-related quality of life (HRQoL), exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. The methods of this RCT have been published in a peer-reviewed journal and are available in Chapter 4. Baseline data collected as part of the RCT were used to compare the physiological and symptom responses of people with CF to two different **laboratory-based exercise tests**. The findings of this comparison are presented in Chapter 5, and the **main results** and discussion of the **RCT** are presented in Chapter 6. Chapter 7 (Part 1) presents a **systematic review** conducted to classify interventions aimed at optimising participation in physical activity as 'promising' or 'not promising' in people aged 15 to 45 years with chronic cardiorespiratory conditions, and categorise the behaviour change techniques (BCTs) within these interventions. Finally, the mapping of the **BCTs** employed within the RCT conducted as part of this research program are reported in Chapter 7 (Part 2).

1.1 Narrative review and meta-analysis (Chapter 2, Part 5)

Exercise training is important in the management of adults with chronic respiratory conditions. Systematic reviews, undertaken in several clinical populations such as adults with chronic obstructive pulmonary disease (COPD) [1, 2], CF [3, 4], non-CF bronchiectasis, interstitial lung diseases (ILDs) [5-7], asthma [8] and non-small cell lung cancer (NSCLC) [9, 10], have shown that exercise training is effective at increasing exercise capacity. Additionally, exercise training has been demonstrated to reduce the severity of symptoms, such as dyspnoea and fatigue experienced during daily life, and improve HRQoL [11]. In the general population, exercising at moderate to high intensity is recommended to optimise the magnitude of improvement in exercise capacity [12]. Consistent with these data, studies of people with COPD suggest that, in contrast with low-intensity exercise, high intensity exercise training may be advantageous in eliciting a physiological training response [13-17]. These data are in keeping with a basic principle of exercise training which states that in order to improve exercise capacity, the load borne by the system during exercise must be progressively increased such that it exceeds that borne during daily life (i.e. the overload principle) [18].

Regarding the mechanisms underpinning the improvements in exercise capacity, in people with COPD for example, these gains are not mediated through improvements in lung function [19-21]. In fact, some of the earliest work done in the area of exercise training for people with COPD [22] was met with scepticism as the gains in exercise capacity were demonstrated without any change in forced expiratory volume in 1 second (FEV_1). In the mid-1990s, seminal work demonstrated that the changes in exercise capacity were mediated by improved condition of the peripheral muscles, largely the vastus lateralis [23]. Although these data exist predominantly for people with COPD, guidelines regarding the prescription of exercise training for people with other chronic respiratory conditions recommend exercise training at moderate intensity or higher [4, 24, 25]. However, achieving high intensity exercise may be challenging for people with a chronic respiratory condition. The reasons for this are multi-factorial. First, people with moderate to severe disease are likely to demonstrate ventilatory limitation to exercise [13, 26], coupled with worsening respiratory mechanics during exercise [14], both of which can constrain the intensity that can be achieve before the onset of intolerable dyspnoea. Second, some people with chronic respiratory conditions who do not qualify for long-term oxygen therapy demonstrate a marked reduction in peripheral capillary oxygen saturation on exertion. This is due largely to ventilation and perfusion mismatch (V/Q mismatch) and is generally more pronounced in people with more

severe respiratory disease [27]. In some clinical populations, such as those with COPD, it is unclear whether treating transient exertional desaturation with supplemental oxygen is of benefit [28]. In other populations, such as those with ILDs, even high-dose supplemental oxygen may not be able to prevent marked desaturation [29, 30]. In the presence of transient exertional desaturation, clinicians may choose to reduce the exercise intensity, which compromises the training dose achieved. Third, many people with chronic respiratory conditions, particularly those who are older, may have comorbidities that contribute to the difficulty of achieving high intensity exercise. These conditions may include osteoarthritis [31], feelings of anxiety and depression [32], or obesity [33]. Given these aforementioned challenges, there has been an interest in applying alternative training approaches such as HIIT as a strategy to optimise the load that can be tolerated during exercise training [34-36].

A solicited review was conducted to answer the following research question: what is the evidence for the effects of land-based whole-body HIIT on exercise capacity in adults living with chronic respiratory conditions, including people with COPD, CF, non-CF bronchiectasis, asthma, ILDs and NSCLC?

This narrative review will be the first to synthesise evidence on the effects of HIIT on exercise capacity in people with chronic respiratory conditions. As such, it will determine the evidence available for HIIT in people with chronic respiratory conditions and determine the gaps in the literature to be investigated in future research. This narrative review will, in part, provide a rationale for the RCT conducted in this program of research (discussed in Chapters 4 to 6).

1.2 Survey (Chapter 3)

Exercise testing and exercise training are important components of the clinical care of people with CF [37, 38]. Regarding testing, international guidelines on the management of people with CF recommend annual laboratory-based exercise testing (i.e. a cardiopulmonary exercise test [CPET]) to identify exercise intolerance, to guide exercise prescription and for prognostication [38, 39]. Nevertheless, in many clinical populations, the uptake of laboratory-based exercise tests is compromised by cost, and the need for specialised equipment and technical expertise to conduct these tests [40, 41]. For example, decade-old data suggests that less than 50% of people with CF living in the United Kingdom and Germany undertake CPETs annually [40, 41]. In contrast to laboratory-based tests, field-based exercise tests, such as the 6-minute walk test or incremental shuttle walk test, are likely to have greater clinical utilisation [42].

Regarding training, clinical guidelines currently recommend that people with CF complete 30 to 60 minutes of moderate intensity aerobic exercise on most days [4]. This recommendation aligns with that made for the general adult population [12, 43, 44]. However, current practices regarding exercise training within Australian and New Zealand CF centres are unclear.

This study sought to answer the following research question: what is the extent and scope of, and importance placed on, exercise testing and exercise training in Australian and New Zealand CF centres?

This survey will be the first to capture the practices of exercise testing and training in CF centres in Australia and New Zealand, and will provide a benchmark of current clinical practice.

1.3 Randomised controlled trial: methods, baseline comparisons and post-intervention findings (Chapters 4 to 6)

Cystic fibrosis is the most common genetic disease and predominantly affects Caucasian people [45]. Increasing treatment options, and a shift to a multidisciplinary approach to care over the last five decades have resulted in a dramatic increase in the life expectancy of people with CF to over 40 years, from 10 years in 1966, to 28 years in 1989 [46]. The increase in life expectancy comes at the cost of a high daily treatment burden. That is, medical, nutritional, and physiotherapy and exercise regimens for people with CF are time consuming and can take up to 4 hours each day [47]. Further, despite the recent improvements in life expectancy, people with CF continue to display reduced exercise capacity compared to the general population [48, 49], experience lower HRQoL, and report rates of anxiety and/or depression two to three times higher than the general population [50]. There are several reasons for the reduction in exercise capacity, including decrements in respiratory function (which arise as a result of mucus plugging, inflammation and scarring within the lungs) and peripheral muscle dysfunction. Improving exercise capacity is an important treatment goal for people with CF, as it may optimise outcomes such as HRQoL [51] and survival [19, 20, 38]. In addition, as shown in the general population, participation in exercise training may have a modifying role on the development and course of anxiety and/or depression [52, 53].

In people with CF, there are data from RCTs of moderate- to high intensity exercise training to show that implementing such a training program is safe and improves outcomes such as exercise capacity and HRQoL [37]. Despite the benefits of exercise training in this population, the recommendation to complete 30 to 60 minutes of moderate intensity aerobic exercise daily [4] may not be possible for people with CF who, consistent with the general population, have competing demands on their time for work, study and family, but who also have a high daily treatment burden [54]. In addition, inactivity and non-participation in exercise may be a mechanism to minimise the onset of intolerable symptoms of dyspnoea and muscle fatigue associated with exercise in people with CF. An alternative training approach such as HIIT may be a more time-efficient and tolerable option to optimise exercise capacity.

High intensity interval training is characterised by short periods of 'work', which are interrupted by periods of 'rest', or lower-intensity exercise. The rest period allows for partial recovery of symptoms such as leg muscle fatigue and dyspnoea, and therefore offers the opportunity to optimise the training intensity that can be tolerated during the work periods [55, 56]. High intensity interval training has been demonstrated to be an effective means of improving exercise capacity within a shorter time frame than traditional 'continuous' exercise training at a moderate intensity in healthy people [57], as well as in people with a chronic cardiorespiratory condition [35]. This type of training may also be more enjoyable than continuous exercise training [58]. Studies suggest that this training approach is feasible and effective in people with CF [34, 59, 60], including those whose condition is characterised by severe expiratory airflow obstruction [34]. To date, there have been no RCTs investigating the effects of HIIT versus usual care on exercise capacity in people with CF. Further research is required to investigate the effects of a low-volume HIIT program in people with CF.

The protocol of the RCT conducted in this program of research is described in Chapter 4. This chapter was published in 2018 [61]. The research questions and significance of Chapters 5 and 6 are described below.

Chapter 5

This study was conducted using baseline data collected as part of the RCT. It sought to answer the following research questions: in adults with CF, (i) how do the physiological and symptom responses during a constant work rate cycle ergometry test compare to those elicited during a maximal incremental ramp-based cycle ergometry test; and (ii) what are the limits of agreement of peak measures during the two cycle ergometry tests?

This analysis is the first to compare the exercise responses and limits of agreement between a traditionally maximal test and a traditionally submaximal exercise test in people with CF. This comprehensive assessment of exercise capacity in people with CF will allow the physiological and symptom responses to two laboratory-based exercise tests to be compared in people with CF.

Chapter 6

The specific research question answered in this chapter was: in people with CF, what was the effect of an 8-week low-volume HIIT program, compared with weekly contact and no formal exercise training, on exercise capacity (primary outcome), HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment (secondary outcomes)?

Secondary research questions also answered were: in people living with CF who were allocated to the experimental group of the RCT, (i) what proportion of participants developed post-exercise quadriceps femoris muscle soreness each week during the 8-week HIIT program, and how severe was this symptom; (ii) how well did the participants tolerate the HIIT program; and (iii) what were the participants' reflections to the facilirators and barriers following the HIIT program?

If 30 minutes of HIIT (i.e. three 10-minute sessions) per week is demonstrated to improve the above-mentioned outcomes, it will represent an achievable and efficient method of exercise training and will thereby overcome the barrier of 'lack of time'. Limitations in the evidence base for the effects of HIIT on exercise capacity in people with chronic respiratory conditions, in particular CF (as highlighted by the narrative review conducted in Chapter 2, Part 5), will be partially overcome by the findings of this RCT.

1.4 Systematic review (Chapter 7, Part 1) and mapping of behaviour change techniques (Chapter 7, Part 2)

Participation in physical activity, which may include engaging in structured exercise, is important for maintaining health and wellbeing in the general population [43]. International societies recommend that adults participate in physical activity or aerobic exercise at a moderate intensity for at least 150 minutes per week, or at a vigorous intensity for at least 75 minutes per week [12, 43]. Adolescents are recommended to participate in at least 60 minutes of moderate-to-vigorous intensity physical activity per day [44]. Despite the numerous physical and psychosocial health benefits of physical activity, as few as 50% of adults and 10% of young people appear to meet the current recommendations for sufficient

participation in physical activity [44, 62]. The reasons for insufficient participation in physical activity in the general population include competing time interests, attitudes and motivation, and environmental factors such as inclement weather [47, 54, 63-65].

In addition to the health benefits attained by the general population, for people with chronic cardiorespiratory conditions, participation in physical activity and exercise may optimise function, improve quality of life, slow the progression of disease and enhance prognosis [19, 20, 51, 66-69]. People with chronic cardiorespiratory conditions, however, participate in less physical activity than their healthy counterparts [54, 70-73]. In addition to barriers experienced by the general population, people with a chronic cardiorespiratory condition are likely to face disease-specific barriers to participation in physical activity, such as the time burden of treatment [47], unpleasant symptoms of breathlessness, and leg muscle and general fatigue during physical activity [63, 74]. Participation in physical activity is of particular concern during 'transitional' years such as adolescence and early adulthood. During this developmental period, peer relationships, disease stigma and an increased level of autonomy become important influencing factors in treatment adherence [75-77]. The presence of data demonstrating a positive relationship between physical activity level in early life and physical activity levels later in life [78-80] suggests that targeting physical activity and exercise behaviour in adolescents and young adults is likely to be important to create positive habits and assist this population throughout the aging process.

To address issues related to poor participation in physical activity, there is growing interest in the use of BCTs, which are the active ingredient(s) of an intervention that aim to modify existing or stimulate new behaviours [81, 82]. Michie et al. [82] designed a universally applicable taxonomy in which 93 individual BCTs are clustered into 16 common groups. This taxonomy – known as BCT Taxonomy v1 – has been applied to research that aims to reduce total sedentary time [83], facilitate smoking cessation [84, 85] and optimise diabetes care [86]. Researchers have yet to apply the taxonomy to understand the BCTs employed in physical activity interventions with adolescents and young adults with chronic cardiorespiratory conditions, including people with CF, who face internal (e.g. motivation and attitudes), external (e.g. competing time interests) and disease-specific barriers to physical activity and exercise [47, 54].

Part 1

Part 1 of this chapter was designed to answer the following research questions: in adolescents and adults with one or more chronic cardiorespiratory conditions, (i) which interventions aimed at optimising participation in physical activity were 'promising' or 'not

promising'; and (ii) which BCTs could be identified and mapped from the 'promising' and 'not promising' interventions?

Part 2

Part 2 of this chapter was designed to answer the following question: in people with CF who were randomly allocated to the experimental group of the RCT conducted in this research program, which BCTs and psychological processes were organically employed to optimise participation in the HIIT intervention?

CHAPTER 2

LITERATURE REVIEW

Overview

This chapter comprises five parts. **Part 1** provides an overview of cystic fibrosis (CF). Information is provided on the: (i) prevalence and incidence of CF, and life expectancy of people with CF; (ii) pathology and pathophysiology of CF, and methods used to diagnose the condition; and (iii) trajectory of airways disease. **Part 2** outlines the impact of CF on important health outcomes, such as exercise capacity, health-related quality of life (HRQoL), exercise self-efficacy and mood. **Part 3** discusses the usual treatment regimen for a person with CF, separated into pharmacological and non-pharmacological treatment components. This section aims to highlight the substantial treatment burden people with CF endure as part of their daily lives. **Part 4** explores the role of exercise training, with a focus on aerobic exercise. **Part 5** includes a solicited narrative review with meta-analysis on high intensity interval training (HIIT) in people with chronic respiratory conditions. This review was accepted for publication in *BMC Sport Science, Medicine and Rehabilitation* in March 2020 [87].

Part 1

The first part of this chapter will provide an introduction to CF, including information on the disease prevalence and incidence, and life expectancy of people with the disease. The pathophysiology, diagnostic tools and disease trajectory will also be reviewed.

2.1 Introduction

2.1.1 Prevalence, incidence and life expectancy

Cystic fibrosis is the most common heritable disease in the western world [88-90]. This disease is estimated to affect over 70,000 people worldwide [91]. In 2015, it was reported that almost 3,500 Australians had a diagnosis of CF, with a further 25% of the Australian population being known 'carriers' of the defective CF transconductance regulator (*CFTR*) gene. That is, 25% of the Australian population had one recessive allele for the disease [92]. In Australia, approximately one in 3,500 live births are diagnosed with CF, with an equal distribution of the disease in males and females [45]. The incidence of CF is variable among ethnic populations, but it is most common in Caucasian people [88].

The life expectancy of people with CF has improved in recent decades [46]. Advancements in multidisciplinary care over the past 50 years have resulted in the current median life expectancy exceeding 46 years for males and 41 years for females with CF [46]. It is projected that people who were born with CF after the year 2000 will survive into their fifth decade of life. Both the current and projected life expectancy have improved substantially when compared to the median life expectancy of 1 year in 1938, 10 years in the 1960s and 28 years in 1989 [93-95]. Similarly, the annual mortality rate has decreased by 21% (hazard ratio 0.8, 95% confidence interval [CI] 0.6 to 1.0) over the last decade due to improvements in multidisciplinary care, growing treatment options and better knowledge of the disease [46, 96]. The improvements in life expectancy come at the cost of a high and rising daily treatment burden. That is, the disease self-management regimens for people with CF, which may involve medical, nutritional and physiotherapy treatment [97], are complex and can take 2 to 4 hours each day to complete [64]. The specific treatment regimens for people with CF will be discussed later in this chapter (Section 2.3).

Several factors may affect survival in people with CF. Some of the predictors of survival include sex [46], a diagnosis of CF-related diabetes (CFRD) [98], the presence of particular microbial agents and delayed diagnosis [99]. The impact of these factors will be briefly reviewed in the following sections.

2.1.1.1 Sex

Despite an equal incidence of the disease in both sexes at birth, males with CF tend to have a survival advantage compared to females with CF [46, 100, 101]. In a study conducted in the United States of America (USA) between 2000 and 2010, males with CF had a 19% (95% CI

13 to 24) lower risk of mortality overall than females with CF over the 10-year period [100]. The reasons for sex-related differences in survival are likely complex and remain poorly understood [100]. Some plausible explanations include that females with CF appear to be more susceptible to recurrent respiratory exacerbation in early life and a more abrupt decline in respiratory function than their male counterparts, leading to poorer survival patterns across the lifespan. Specifically, a retrospective study using CF Foundation Patient Registry data for 32,766 people with CF born between 1958 and 2007 in the USA demonstrated that females were more likely to acquire hazardous microbial agents such as *Pseudomonas aeruginosa* (*P. aeruginosa*) and the *Burkholderia cepacia* complex (BCC) earlier in life than males. For *P. aeruginosa*, the mean age at first culture for males (n = 8,442) was 13 ± 9 years, compared to 10 ± 9 years for females (n = 10,222) (multivariate Cox regression for survival [95% CI] 1.6 [1.4 to 1.8], $p < 0.001$). The above-mentioned microbials are known to be associated with poorer respiratory outcomes and survival in people with CF. The cause of this sex discrepancy related to microbes is not clear. However, prevention of colonisation in the first instance continues to be an important treatment goal [102]. Another possible explanation for the survival disparity between sexes may be explained by the presence of oestrogen and other female hormones, or the absence of male sex hormones such as testosterone. Although the mechanisms behind these potential sex hormone effects are also unclear [103], one possible explanation is that testosterone may have a protective effect on muscle mass in males.

2.1.1.2 Cystic fibrosis–related diabetes

Cystic fibrosis–related diabetes affects approximately 20 to 30% of people with CF worldwide [104-106] with a similar prevalence reported in Australia [45]. The likelihood of developing CFRD rises with increasing age [45, 107] and being diagnosed with CF gene mutations that are categorised as more ‘severe’ [108]. People diagnosed with CFRD have a poorer prognosis than those without CFRD [109]. However, the risk of mortality associated with CFRD has reduced. Registry data from the USA shows that 17% of people with a diagnosis of CRFD between 1992 and 1997 died, compared to 3% between 2003 and 2008 [110]. Cystic fibrosis–related diabetes shares pathophysiological components of both type 1 and type 2 diabetes. For example, pancreatic scarring, inflammation and loss of β cells impairs the production of insulin [111], leading to insulin deficiency (i.e. type 1 diabetes), whereas the chronic use of certain medications is linked with insulin resistance (i.e. type 2 diabetes) [112, 113]. The presence of hyperglycaemia related to CFRD is associated with poorer clinical outcomes including malnutrition, increased inflammation and risk of respiratory exacerbations, poorer respiratory function, and reduced survival [108, 112].

2.1.1.3 Pathogens and colonisation

Exposure to various pathogens and bacteria is common across the lifespan for the general population. Exposure can be environmental in nature (i.e. contact with contaminated water or drain pipes), or via person-to-person transmission (i.e. coughing, sneezing or talking) [114]. In healthy people, exposure is unlikely to be threatening because pathogens are rapidly removed from the body by the immune system, without initiation of a substantial inflammatory response. In otherwise healthy people, two main mechanisms remove pathogens from the respiratory system: (i) mechanical removal (i.e. mucociliary clearance), and (ii) macrophages and antimicrobial peptides [115]. In people with CF, pathogens can be difficult to eradicate due to impairments in the above-mentioned systems and may require antibiotic assistance. In addition, pathogens can become resistant to treatment due to impaired mucociliary clearance, which persists as a result of excessive mucus load, inflammation and scarring within the lungs [116]. Chronic infection with pathogens in the respiratory system is referred to as 'colonisation'.

Across their lifespan, people with CF are at risk of becoming colonised with a vast and dynamic array of pathogens [117-119]. Some of the most detrimental pathogens are reported to be BCC, methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, nontuberculous mycobacteria (NTM), methicillin-susceptible *S. aureus* (MSSA), *P. aeruginosa*, *Mycobacterium abscessus* complex, and *Aspergillius fumigatus*. Colonisation with *P. aeruginosa*, for example, is associated with more severe decrements in respiratory function, more frequent respiratory exacerbations and worse clinical outcomes [117, 120]. An analysis was conducted using European CF Society Patient Registry data (n = 14,732) to investigate associations between decline in respiratory function and clinical outcomes [121]. After adjusting for a number of potential confounding factors such as age, country of origin, sex and a diagnosis of CFRD, forced expiratory volume in 1 second (FEV_1) was 13% lower (95% CI 12 to 14) in people who were colonised with *P. aeruginosa* than in people who were not colonised with this microbe, and colonisation with *P. aeruginosa* increased the likelihood of severe respiratory disease (odds ratio [OR] 2.4, 5% CI 2.0 to 2.7) [121]. Similarly, people who are colonised with MRSA appear more likely to have lower respiratory function and/or more rapid decline of their respiratory function than people who are not [122]. Stringent infection control principles in hospitals and CF centres are paramount to prevent the iatrogenic spread of these pathogens from person to person [114, 123].

2.1.1.4 Late diagnosis

While most people with CF are diagnosed early in life, late diagnosis of CF can occur for a number of reasons. These reasons may include *CFTR* mutations that are characterised by 'partial' function of the gene, a false negative at newborn screening or, more rarely, newborn screening not being undertaken. Once CF is suspected, confirmation of the diagnosis by a laboratory sweat test can be difficult in the presence of a rare or atypical *CFTR* mutation and/or lack of clinical features of the condition [124]. A higher proportion of people with a late diagnosis of CF are female (3:1), and are colonised with NTM (versus 10% in people who were diagnosed with CF as a newborn) [125]. Other groups have speculated that NTM may elicit changes in the phenotype of people with CF who previously had minimal to no symptoms [125]. Further research is required to ascertain the cause of the discrepancy in the proportion of males and females who are diagnosed with CF later in life.

There is some evidence that a late diagnosis of CF results in poorer outcomes associated with respiratory disease (in terms of microbial colonisation and respiratory function) [99]. A retrospective analysis of the Australian CF Data Registry (New South Wales sector) between 1988 and 2010 found a total of 45 cases of late diagnosis of CF. These recorded cases of late diagnosis were matched for age, sex, location and pancreatic status with participants of the registry with a confirmed diagnosis of CF by newborn screening. In the registry participants with a late diagnosis of CF, the median number of hospitalisations for respiratory exacerbations per year was higher than in participants who were diagnosed with CF at birth (median [interquartile range; IQR] 0.5, [0.2, 1.1] compared to 0.2 [0, 0.5]). Longer hospital admissions were also recorded for these exacerbations in the participants who had a late diagnosis of CF [99]. In addition, the rates of *P. aeruginosa* colonisation were higher in the participants who were diagnosed later in life, compared to at those diagnosed at birth (mean difference [MD] 23%, 95% CI 54 to 77) [99]. Despite these respiratory manifestations, participants of the registry who were diagnosed later in life appeared to have similar pancreatic function (60% prevalence of pancreatic insufficiency in both groups). In contrast, others have reported that people with a late diagnosis of CF are more likely to have preserved pancreatic function, especially those with a very late diagnosis (i.e. in the third decade of life) [125]. Nevertheless, the psychological ramifications of late diagnosis are likely to be high, and may include stress, emotional trauma and mental health sequelae, breakdown of personal and professional relationships, and economic loss.

2.1.2 Pathology, pathophysiology and diagnosis

Cystic fibrosis is a monogenetic autosomal recessive condition caused by a mutation of the *CFTR* gene [126-128] located on the long arm of chromosome 7 [116, 129, 130]. The CFTR exists on the apical surface of exocrine glands, such as the respiratory epithelium, pancreas, liver and male reproductive system, as well as in smooth, cardiac and potentially skeletal muscle [116, 128]. The CFTR is responsible for the production of saliva, sweat, tears and mucus. In the general population, the *CFTR* gene, a glycoprotein that acts as a cyclic adenosine monophosphate (cAMP) activated chloride (Cl^-) and bicarbonate (HCO_3^-) channel, has a number of functions including mediating the transport of Cl^- and HCO_3^-, and controlling the absorption of sodium (Na^+), resulting in appropriate hydration of the airway surfaces and normal mucus clearance [116].

Hydration of the airways is important in maintaining the movement of mucus along the cilia of the airway epithelium [131]. A defective CFTR, due to insufficient gating, conductance or stability of the aforementioned channels, results in impaired transport of Cl^-, Na^+ hyperabsorption [128] and dysfunction of the epithelial defence mechanisms [132]. These insufficiencies cause increased viscosity of mucus and the breakdown of cilia, which further impairs the removal of mucus from the airways and other exocrine organs. On a macroscopic level, the build-up and 'plugging' of this mucus within the respiratory system results in ongoing inflammation and recurrent infection, which, over time, reduces the elasticity of the airway, causing permanent dilatation (referred to as 'CF-related bronchiectasis') [116, 128, 133]. Recurrent, exaggerated inflammatory responses and an abnormally high sputum load [134], as well as the high presence of neutrophils and inflammatory cytokines, are hallmarks of the progressive damage to the respiratory system. In addition, with increasing disease severity comes an increased likelihood of secondary disease complications, namely pneumothorax, haemoptysis and respiratory failure [133].

Cystic fibrosis is most commonly diagnosed via newborn screening at 3 to 5 days of age, with a repeat 'confirmation' test 4 to 6 weeks later in those for whom the initial test returned a positive result [135]. In a large number of infants (64%) who have a positive newborn screening however, symptoms typical of CF may be absent or negligible [124]. The absence of symptoms in these early stages leads to diagnostic uncertainty [124]. Therefore, the most recent guidelines pertaining to the diagnosis of CF stipulate that positive newborn screening should be accompanied by a positive sweat test, and subsequent testing may be required in the event of borderline sweat test results [124].

2.1.3 Disease trajectory

To manage respiratory health and prevent decrements in respiratory function, guidelines recommend regular measurement of respiratory function in people with CF [136, 137]. The definition of mild, moderate and severe respiratory disease varies within the literature. When measuring severity of respiratory disease using spirometry, an FEV_1 of at least 60% or 70% of the predicted value for the healthy population usually indicates mild respiratory disease; an FEV_1 between 40% and 59% (or 69%) of predicted value usually indicates moderate respiratory disease; and an FEV_1 of less than 40% of predicted value usually indicates severe respiratory disease [138, 139]. Some consider an FEV_1 of less than 30% of the predicted value to be very severe respiratory disease. Despite its wide acceptance, spirometry measurements are effort dependent, variable and poorly responsive [138].

Generally, after the age of six, respiratory function, measured using % predicted FEV_1, declines by 1% to 3% per year in people with CF [138, 140]. Respiratory function remains relatively stable until a person reaches their early- to mid-adolescent years, at which time they are at risk of steeper respiratory function decline, compared to children and middle-aged adults with CF [140]. In a multicentre epidemiological study of European Society of CF data, the most abrupt decline in % predicted FEV_1 occurred between the ages of 11 and 16 [140]. In addition to the predicted 'usual' annual respiratory decline, people with CF may experience frequent and recurrent respiratory 'exacerbations'. There is little consensus on the definition of exacerbations in people with CF. However, symptoms that may be indicative of a respiratory exacerbation in this population include increased sputum volume, changes in the characteristics of sputum, blood present in the sputum, increased cough, pain from coughing, new or increased wheeze, new or increased chest tightness, dyspnoea or increased difficulty breathing, increased fatigue or lethargy, fever, loss of appetite or body weight, sinus pain or tenderness, and increased absenteeism from school or work [141]. It is well established that recurrent and frequent respiratory exacerbations are detrimental to the overall health and survival of people with CF [142], as a respiratory exacerbation can result in more dramatic reductions in respiratory function than the estimated annual decline. This decline can be hastened in the event of a delay in seeking medical assistance [143]. Further, despite optimal multidisciplinary management of their exacerbation, a high proportion of people with CF fail to return to their 'best' respiratory function following an exacerbation of respiratory disease [143]. In a multicentre study conducted in the USA (Standardised Treatment of Pulmonary Exacerbations [STOP] Study) of 220 participants who were admitted to hospital for a respiratory exacerbation, 61% of participants did not recover their lost lung function by 28 days after the event, despite inpatient treatment being deemed

'successful' by a physician [143, 144]. This reduction in respiratory function following an exacerbation negatively impacts on HRQoL, an outcome that has been shown to take several weeks to return to the pre-exacerbation level [145]. Evidence for the effect of exacerbations on markers of exercise capacity is scant and further investigation would be beneficial.

It is important to acknowledge the impact on gene-modifying medication on disease trajectory in people with CF. This will be discussed further in section 2.3.1.

Part 2

Part 2 of the literature review outlines the impact of CF on health outcomes, such as exercise capacity, HRQoL, exercise self-efficacy and mood. Common tools used to measure each outcome will also be reviewed. These outcomes are relevant to future chapters (4 to 6) within this program of research. There is an emphasis on exercise capacity as this is the primary outcome within the aforementioned chapters.

2.2 Impact of cystic fibrosis on health outcomes

2.2.1 Exercise capacity

Impaired exercise capacity is a hallmark of CF [48]. The largest controlled study investigating the prevalence of exercise intolerance in adults with CF, included 64 participants with CF (mean ± standard deviation [SD]: aged 26 ± 8 years, FEV_1 65 ± 19% of the predicted value for healthy people) and 20 healthy controls balanced for age and gender. When compared to healthy controls, the peak rate of oxygen uptake (VO_{2peak}) of participants with CF was reported as 41% (95% CI 32 to 50) lower, and their 6-minute walk distance (6MWD) was reduced by 16% (95% CI 12 to 21) [48]. The cause of reduced exercise capacity is multi-factorial. Reductions in exercise capacity may be caused, in part, by the obstructive nature of the respiratory disease that arises as a consequence of compromised mucociliary clearance, leading to recurrent inflammation and mucus plugging in the airways [39]. People with CF, particularly those with more advanced respiratory disease, may exhibit ventilatory limitation (i.e. during exercise, the peak minute ventilation ($L \cdot min^{-1}$) [V_{Epeak}] encroaches on or exceeds the maximal voluntary ventilation [39, 146]. Furthermore, people with CF may display ventilatory inefficiencies such as a high ratio of dead space to tidal volume (V_D/V_T) during exercise. This in turn increases the load on the respiratory system during exercise [39]. In addition, a high proportion of people with CF can demonstrate dynamic hyperinflation on exertion. In 109 people with CF (aged 30 ± 10 years, 64% male) with mild to moderate respiratory disease (FEV_1 72 ± 18% predicted), almost 60% displayed

dynamic hyperinflation during exercise, and this finding was more pronounced at higher exercise intensities [147]. In this retrospective study, the presence of dynamic hyperinflation was associated with lower respiratory function and heightened level of dyspnoea (Borg dyspnoea at peak exercise 7 ± 3 for people with dynamic hyperinflation compared to 5 ± 2 for people without dynamic hyperinflation). Symptoms of leg muscle fatigue were slightly lower in the people who displayed dynamic hyperinflation at peak exercise (Borg leg muscle fatigue 7 ± 2 compared to 8 ± 3 in those without dynamic hyperinflation), which may be because greater ventilatory impairments in this group led to lower exercise capacity and lower exercise intensity being reached [147]. Symptoms of dyspnoea and muscle fatigue are a common complaint of people with CF during exercise, particularly continuous exercise [60]. These symptoms are reported at lower exercise intensities than tolerated by the general population and can present a barrier to participating in physical activity and exercise for people with CF, resulting in a cycle of physical deconditioning [148].

Earlier work has demonstrated that people with CF, across the continuum of age and disease severity, display impairments of the peripheral muscles compared to the general population [48, 149, 150]. These impairments have been classified by measuring peripheral muscle strength (lower quadricep muscle strength in people with CF compared to healthy controls: MD 25% predicted, 95% CI 16 to 33) [48] and lean muscle mass of the upper and lower limbs (lower mass as a percentage of total body weight in people with CF compared to healthy controls: MD −9%, 95% CI −16 to −2) [151]. There is conflicting evidence about whether people with CF have impairments in muscle endurance and fatigability [150, 152]. A number of factors have been proposed as potential extrinsic causes of peripheral muscle dysfunction, such as the nutritional status of people with CF and the use of corticosteroids [153]. However, there are also data to suggest that the dysfunction may be intrinsic to the disease. For example, muscle dysfunction in people with CF may be related to the reduced blood flow to the skeletal muscle (or 'blood steal') during exercise to compensate for excessive ventilatory requirements [154]. While impaired blood flow responses have been demonstrated at near maximal exercise intensities in the healthy population [154], there are some preliminary data to support that this impairment may be measurable at lower exercise intensities in people with CF. In a recent study by Tucker and colleagues [155], maximal (i.e. VO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$, % predicted and as a proportion of fat free mass) and submaximal exercise capacity (at 60% peak work rate [W_{peak}]) on a cycle ergometer were measured in paediatric participants (n = 14; aged 14 ± 3 years) with mild CF (FEV_1 93 ± 16% predicted) and a demographically matched control group (n = 14). Brachial artery blood flow (diameter and velocity) was measured via Doppler ultrasound during submaximal exercise. Results showed a tendency for blood flow during submaximal exercise to be

impaired among the participants with CF when compared with the control group (MD −22 mL/min, 95% CI −45 to 1). This study was completed in a paediatric population with mild respiratory disease and therefore further studies are required to determine if the results can be extrapolated to adults and across the spectrum of disease severity. In addition, further investigation of femoral artery blood flow and concurrent ventilatory muscle demand is warranted [154].

Another explanation for CF-related intrinsic muscle dysfunction relates to altered mitochondrial function or a mitochondrial defect in the skeletal muscle (identified using magnetic resonance spectroscopy) and vascular endothelial cells [156]. More recently, intrinsic muscle dysfunction has been hypothesised to relate to the *CFTR* gene itself. It was originally proposed that the defective *CFTR* gene was only present in exocrine glands such as the lungs, pancreas, liver and male reproductive system, but more recently the defective gene has been identified in the sarcotubular network, sarcolemma and sarcoplasmic reticulum of skeletal muscle in mice models and human models [157, 158]. A defective *CFTR* gene in skeletal muscle can impair ion transport, leading to inappropriate contraction and relaxation of actin and myosin filaments within the muscle fibre. Despite these findings supporting the presence and function of the CFTR in the skeletal muscle of animals, it remains difficult to reproduce these findings clinically and across various ages and disease severities in people with CF [159]. Regardless of the cause of impairment in the peripheral muscles, a moderately strong relationship exists between quadriceps muscle force and VO_{2peak} ($r = 0.55$, $p < 0.001$) [48].

A final cause of impaired exercise capacity in people with CF may be related to cardiac impairments, such as an inability to increase their stroke volume or the onset of cor pulmonale, particularly during the end stages of the disease [39, 160]. Irrespective of the mechanism, ventilatory limitation and muscle impairments are demonstrated during exercise in people with CF, and these are likely to explain why people with CF, regardless of disease severity, report symptoms of leg muscle fatigue to be worse than dyspnoea during cycling-based exercise [148, 152].

2.2.1.1 Measurement

Exercise capacity can be measured using laboratory- or field-based tests. Expert consensus from international groups recommends that, where possible, people with CF aged 10 years or older should undertake an exercise test at least yearly. If equipment and resources permit, these tests should be laboratory-based [161]. Data from these exercise tests can be used to prescribe an exercise program, evaluate the effectiveness of interventions on exercise

capacity and provide information on prognosis [42, 161]. Despite the usefulness and perceived importance placed on exercise testing by CF clinics, exercise testing, particularly laboratory-based tests, are underutilised in this population in the United Kingdom (UK), Germany and Australasia [40, 41, 162]. A survey of exercise testing practices in Australia and New Zealand CF centres is included in Chapter 3 of this program of research.

Laboratory-based tests

The cardiopulmonary exercise test (CPET) is a comprehensive and reproducible method of evaluating exercise capacity and the cause of impairments in people with CF [163]. Cardiopulmonary exercise tests can be used to: (i) determine the cause of the limitation in exercise capacity, for example, respiratory, cardiovascular, muscular and motivational factors; (ii) quantify disease progression or estimated survival [19, 20, 38]; (iii) determine response to therapy, for example, exercise training [42]; (iv) assess pre-operative or anaesthetic risk [164]; and (v) prescribe the intensity of exercise training [37]. Of note, measures collected during a CPET, such as VO_{2peak}, W_{peak} and minute ventilation/rate of carbon dioxide production (VE/VCO_2), may be more robust indicators of disease severity and, ultimately, survival than respiratory function measures collected using spirometry (i.e. FEV_1) [38]. These measures collected during a CPET are also used in people with CF to determine the suitability for lung transplantation [38].

Cardiopulmonary exercise tests are commonly performed on a cycle ergometer or treadmill. The cycle ergometry test may be preferred because the equipment requires less space, and the workload or 'intensity' can be set on a cycle ergometer, unlike on a treadmill where intensity must be estimated. Further, cycle ergometry tests are less influenced by movement or 'noise', leading to higher quality data [164]. In each of these systems, the following physiological responses are measured continuously or at regular intervals: heart rate (HR) (using a 12-lead electrocardiogram), peripheral capillary oxygen saturation (SpO_2), breath-by-breath measurements of oxygen uptake (VO_2) and VCO_2, blood pressure, and symptom response (breathlessness, leg muscle fatigue, or rate of perceived exertion using a Borg or modified Borg scale) [39, 42, 164].

One of the most commonly used protocols to perform a CPET is a maximal incremental exercise test to volitional exhaustion. For this type of protocol, the CPET usually begins with a period of 'rest', followed by a period of unloaded exercise, a 'work' phase and a 'recovery' phase. During each phase, it is recommended that standardised instructions be provided in order to encourage the person to reach a maximal effort by the end of the test. The work phase of this type of test can be 'ramp-based', meaning the workload is gradually increased by a set number of Watts each minute, or 'step-wise', whereby the chosen workload is

progressively added at a single time point (the start of each minute) [164]. Patient self-reported data on usual exercise participation and clinical expertise are used to determine the amount that the work rate is set to increase by each minute [164, 165], with the aim of achieving a work phase of 8 to 12 minutes [42, 164]. Exercise capacity is usually reported as the VO_{2peak} or W_{peak} achieved during a ramp-based cycle ergometry test [38].

A submaximal, constant work rate cycle ergometry test can be used to measure endurance exercise capacity. In this test, a person is asked to cycle at a set work rate (i.e. 70 to 80% of the W_{peak} achieved during a CPET) until the point of symptom limitation or until volitional exhaustion. In keeping with the maximal CPET, the constant work rate cycle ergometry test also involves the following phases: (i) rest; (ii) unloaded exercise; (iii) work; and (iv) recovery phase [42, 165, 166]. In people with chronic obstructive pulmonary disease (COPD), constant work rate cycle ergometry tests are widely accepted to be the most responsive laboratory-based exercise tests for detecting changes in exercise performance after a program of exercise training [167]. Further, in people with CF, the intensity of submaximal exercise tests may better reflect activities of daily living [168]. Despite the acceptance of constant work rate cycle ergometry tests in populations with other chronic respiratory conditions, such as COPD, data pertaining to the physiological responses and sensitivity of this test to detect changes in people with CF are limited [169]. Nevertheless, there are data indicating that the results of this test are repeatable in people with CF. Specifically, in a sample of seven young adult males with CF (aged 26 ± 9 years, FEV_1 64 ± 23% predicted), the coefficient of variation for time to symptom limitation (T_{lim}) in a constant work rate cycle ergometry test done at 80% of W_{peak} was 5.7% (within-subject over time, calculated at the end of exercise), indicating that this measure had high repeatability. It is important to note that this magnitude of variation was similar to that for FEV_1 [170]. In addition to the T_{lim}, the coefficient of variation of other variables recorded during the constant work rate cycle ergometry tests (i.e. VO_2, V_E, HR, SpO_2) were less than 5.0%. As there are limited data pertaining to the constant work rate exercise test in people with CF, cardiorespiratory and symptom responses during the ramp-based and constant work rate cycle ergometry tests were compared as part of this program of research (Chapter 5). The responsiveness of the constant work rate cycle ergometry test was also investigated in the randomised controlled trial (RCT) of this program of research (Chapter 6).

Field-based tests

Compared to laboratory-based exercise tests, field-based exercise tests are cost-effective and relatively easy to complete in clinical practice due to the portable nature of the equipment required. In Australia, the most commonly performed field-based exercise tests in people

with CF include the 6-minute walk test (6MWT) [171] and the incremental shuttle walk test (ISWT) [162] (see Chapter 3). The most common physiological measurements collected during these field-based tests are HR and SpO_2. Unlike laboratory-based exercise tests, in clinical practice, measures of gas exchange and ventilatory parameters are not collected.

Field-based exercise tests are not included as outcome measures within the studies completed as part of this program of research. For completeness, the following section describes some of the most commonly performed field-based exercise tests in people with CF (6MWT and ISWT). Brief comment will also be made on less commonly performed field-based exercise tests [162].

The 6MWT [172] is perhaps the most commonly utilised field-based walking test in the CF population. During this test, people are asked to cover as much ground as possible and are therefore walking at the maximum speed they believe is sustainable over a 6-minute period. The primary outcome of this test is the distance walked, but often other data are collected such as HR, SpO_2 and symptoms (rate of perceived exertion, dyspnoea and/or leg muscle fatigue). While these tests require health professionals to follow a strict protocol to ensure standardisation, they do not require expensive laboratory-based equipment, making it a feasible test to complete in clinical practice. Previous studies have demonstrated reproducibility of the 6MWT in adolescents and adults with CF provided that two tests are completed, and compared, on a single testing occasion [171]. In 31 people with CF (aged 24 ± 7 years, FEV_1 61 ± 28% predicted), the coefficient of variation calculated at the end of the tests (within-subject over time) was 4.3%. However, in the above-mentioned study, the mean difference (MD) between testing time points was −7 m, with wide limits of agreement between the two tests (−75 to 62 m). Thus, two tests are recommended [171]. The 6MWT may provide prognostic information in adults with CF, particularly in people who exhibit marked oxygen desaturation (SpO_2 < 90%) and lower FEV_1 [173]. Despite the potential prognostic information derived from the 6MWT, people with mild to moderate respiratory disease may encounter a ‘ceiling effect’; that is, they may be limited by the protocol instructing participants not to run during this test. This ceiling effect is highlighted in a study of 50 people with CF (aged 14 ± 4 years [range 7 to 25 years], FEV_1 88 ± 19% predicted), whereby the MD between the 6MWT and the ISWT distance was 122 m in favour of the ISWT. Additionally, people with CF are less likely to reach a high intensity of exercise by the end of the 6MWT, based on physiological and symptom parameters (end-test percentage of maximal heart rate [HR_{max}] was 63 ± 12% in the 6MWT compared to 84 ± 8% in the ISWT; end-test dyspnoea was 2 ± 2 for the 6MWT compared to 3 ± 2 for the ISWT). As

such, in people with mild disease, the 6MWT has a ceiling effect and the distance walked is likely to be related more closely to stride length, which makes the test less responsive [174].

The ISWT is an externally paced test that is designed to elicit maximal stress on the respiratory, cardiovascular and musculoskeletal systems. This test is performed on a 10 m flat walk track, demarcated by two cones placed 9 m apart. The person needs to walk between the cones at a speed dictated by an audio-recording. The speed progressively increases each minute and the person is instructed to continue until they can no longer keep up with the set speed due to the onset of intolerable symptoms. In contrast with the 6MWT, at the highest speeds during an ISWT the person is permitted to run and is therefore less likely to experience a 'ceiling effect' [174]. As with the 6MWT, the primary outcome recorded for the ISWT is the distance covered, but other measures (HR, SpO_2 and symptoms) are also often made.

Alternative field-based exercise tests such as the endurance shuttle walk tests and the Alfred Step Test have been less commonly reported [162, 175-177]. The Alfred Step Test appears to be a valid and reliable measure of exercise tolerance in children with CF [175, 176], and has demonstrated high validity and reliability in adults with CF and a variety of disease severities [177].

2.2.2 Health-related quality of life

Health-related quality of life can be defined as "how well a person functions in their life and their perceived wellbeing in physical, mental and social domains of health" [178, 179]. While the life expectancy of people with CF is improving, so is the complexity of disease self-management and the daily treatment burden, which can negatively impact HRQoL [47, 64] (discussed further in Part 3 of this chapter). In addition to the usual burden of disease, extrapulmonary comorbidities such as CFRD, osteoporosis, liver and kidney disease, anxiety and/or depression, and pain are likely to manifest themselves throughout the lifespan, adding to the complexity of CF disease management [180]. Additionally, sex (i.e. females tend to report lower HRQoL), employment status, socioeconomic status, ethnicity and sleep quality play a role in the level of perceived HRQoL in people with CF [181-183]. In a longitudinal study, Abbott and colleagues assessed the progression of HRQoL over the course of a decade in people with CF (aged 25 ± 7 years, FEV_1 59 ± 24% predicted at the commencement of the study), and the relationship between self-reported HRQoL and respiratory function, measured as FEV_1 % predicted. This study demonstrated that decrements in respiratory function were weakly associated with decrements in HRQoL [184]. This relationship was the strongest for the HRQoL domains of physical function (coefficient: −0.2, $p < 0.001$), chest

symptoms (coefficient: 0.17, $p < 0.001$), career concerns (coefficient: −0.16, $p < 0.001$) and social functioning (coefficient: −0.13, $p = 0.004$). Similar data have been reported elsewhere. When grouped according to their level of disease severity (mild, moderate or severe), people with CF (n = 223, aged 25 ± 7 years, FEV_1 55 ± 24% predicted) demonstrated worsening HRQoL as disease severity increased. In addition to the relationship between respiratory function and HRQoL, there was a modest positive relationship between HRQoL and VO_{2peak} (r = 0.30 to 0.46), as well as peak power (r = 0.24 to 0.35) [51]. Given HRQoL is arguably the most important patient-reported outcome, it is an end-point for the evaluation of interventional effectiveness [185].

2.2.2.1 Measurement

Although a number of generic and disease-specific tools are available to measure HRQoL in people with CF [185], there is no consensus on the optimal method. Generic HRQoL questionnaires, such as the Short Form 36 (SF36) have been validated in the CF population, but, as seen in many other clinical populations, disease-specific scales are more responsive to change and should be used where possible [185, 186]. Disease-specific HRQoL measures include the CF Questionnaire (CFQ) and the revised version (CFQ-R) [187]. Most recently, the Alfred Wellness Score for CF (AweScore-CF) [188] has been produced to measure 'wellness' in this population. The CFQ-R and AweScore-CF will be discussed in this section.

The CFQ-R is arguably the most widely utilised and validated [189] outcome measure of HRQoL for use in people with CF. The psychometric properties of the CFQ-R were assessed by conducting a multicentre, longitudinal, epidemiological study of 7,330 participants across the lifespan (aged 6 to 70 years). The findings of this large study demonstrated high internal consistency (Cronbach α: 0.70), and strong discriminant validity between well and unwell states (between-stage difference in all domains except 'digestive symptoms') and severity of respiratory disease [189]. The CFQ-R comprises 50 questions divided into 12 domains: physical function (eight items), vitality (four items), emotional function (five items), eating disturbance (three items), treatment burden (three items), general health perception (three items), social function (six items), body image (three items), role limitations (four items), weight problems (one item), respiratory symptoms (six items) and digestive symptoms (three items). Each question of the CFQ-R is answered on a four-point Likert scale, from 'always' (a score of one) to 'never' (a score of four), or 'a lot of difficulty' (a score of one) to 'no difficulty' (a score of four). Higher scores indicate better perceived HRQoL, with a total score out of 100. The CFQ-R is available in a variety of languages, including English and

German. However, the CFQ-R questionnaire is five pages in length and takes approximately 15 minutes to complete [187, 189].

The AweScore-CF was developed more recently by Button and colleagues in Melbourne, Australia, with the aim of reducing the complexity and time burden required to complete a HRQoL questionnaire [188]. The single-page questionnaire incorporates 10 items on wellness, with a 1 (least well state) to 10 (most well state) visual analogue scale used to answer each question. The AweScore-CF takes a few minutes to complete and a score of 100 indicates 'perfect' wellness. The 10 items are related to coughing in the past 24 hours, sputum volume, energy levels, exercise participation, appetite, weight, mood, anxiety, sleep amount/quality and general health. The AweScore-CF is a well-accepted, quick and easy to complete tool for assessing wellness in people with CF. This questionnaire was found to be reliable in the inpatient and outpatient setting, where participants were asked to complete two questionnaires across a 24-hour period (correlation: 0.99, 95% CI 0.98 to 0.99, limits of agreement −5.0 to 4.6) [188, 190].

2.2.3 Exercise self-efficacy

Self-efficacy is defined as the self-belief that a person is capable of undertaking and maintaining a behaviour, such as participation in regular exercise. Self-efficacy is derived from three main elements: (i) beliefs; (ii) level of motivation; and (iii) previous accomplishments. This construct, originally determined by Bandura, does not consider whether a person is able to master a new skill or maintain a behaviour, but rather whether the person believes that they are able to [191, 192]. People who report higher self-efficacy are more likely to initiate or maintain a new behaviour (e.g. exercise) in the long term [193], despite being faced with potential barriers or challenges [192, 194]. Therefore, measurement of self-efficacy is an important consideration when investigating the effectiveness of an intervention such as exercise training [193]. While research into the factors influencing exercise participation in people with CF is in its infancy, exercise self-efficacy (i.e. confidence to exercise) has been established as an independent predictor of 'intention' to exercise [195].

2.2.3.1 Measurement

There are currently no CF-specific tools available to measure exercise self-efficacy and no consensus on the optimal measurement tool. The Barriers Self-Efficacy Scale (BARSE) [194] is a 13-item generic exercise self-efficacy questionnaire. The questionnaire uses an 11-point scale to report on whether a person believes they could exercise three times per week

for the next 3 months considering a number of common barriers to undertaking exercise, for example, if the weather was bad or they were on holiday. Each question is scored using a 100-point percentage scale, with 0% representing 'not confident at all' and 100% representing 'highly confident'. The average of the scores is calculated (total score out of 100), with a higher score indicating better exercise self-efficacy [194]. Other tools have been used to measure exercise self-efficacy in clinical groups, such as the Self-Efficacy for Exercise Scale (SEE) [196] and the Exercise Self-Efficacy Scale (EXSE) [193]. However, unlike the BARSE, these alternate questionnaires do not take into account common barriers that may prevent people from participating in exercise, such as the weather, exercise location and personal stress. In addition, it has been postulated that some of the barriers listed within the BARSE were likely to be particularly relevant to people with CF, such as 'I felt pain or discomfort when exercising', 'I was self-conscious about my appearance when I exercised' and 'my schedule conflicted with my exercise session'.

2.2.4 Feelings of anxiety and depression

Feelings of anxiety and depression are commonly reported by people with a variety of chronic medical conditions [197-199]. In particular, meta-analysis has demonstrated that people who have a chronic respiratory condition, such as COPD, are more likely to develop depression than the general population (pooled OR: 3; 95% CI: 2 to 5) [200]. The prevalence of anxiety and depression in people with COPD is 26% [201]. People with CF are at a high risk of developing feelings of anxiety and depression over the course of their lifespan, related not only to symptoms and impairments of the disease, but also the high daily treatment burden [50]. In comparison to people with COPD, approximately 30% of children and almost 50% of adults [202] with CF report feelings of anxiety and depression [50]. Symptoms of depression are negatively associated with lower respiratory function and lower levels of physical activity [203]. In addition, feelings of anxiety and depression are associated with negative clinical outcomes, including poor adherence to treatment, worse symptoms and/or respiratory function [202], increased healthcare costs [50], and impaired HRQoL (anxiety: $r^2 = 0.16$, $p = 0.005$; depression: $r^2 = 0.40$, $p < 0.001$) [202].

The International Depression/Anxiety Epidemiological Study (TIDES) was conducted in 154 CF centres across nine countries in Europe (including Belgium, Germany, Spain, Sweden, The Netherlands, Turkey and the UK) and the USA, making it the largest psychological screening study conducted in people with chronic respiratory condition to date [50]. The study involved people with CF aged ≥12 years (n = 6,088; n = 1,286 adolescents [aged 15 ± 2 years] and 4,739 adults [aged 29 ± 10 years]), as well as caregivers of people with CF (n = 4,102). Feelings of anxiety and depression were measured using the Hospital

Anxiety and Depression Scale (HADS) [204] and the Centre for Epidemiologic Studies – Depression Scale (CES-D) [205]. Feelings of anxiety were present in 22% of adolescents and 32% of adults with CF, and feelings of depression were reported in 10% of adolescents and 19% of adults. Further, people who experienced feelings of anxiety had higher odds of reporting feelings of depression (OR for adolescents = 15 and for adults = 14 [95% confidence intervals not reported]) [50]. In people with CF, factors that have been shown to influence the likelihood of developing feelings of anxiety and/or depression are older age, female sex, the severity of respiratory disease and/or recent acute worsening in health status [202]. Due to the high impact on other clinically important outcomes, such as respiratory function, HRQoL, physical function and treatment adherence, the International Committee on Mental Health in CF now recommend routine annual screening for anxiety and depression [206].

2.2.4.1 Measurement

In the absence of a 'gold-standard' diagnostic measure for anxiety and/or depression in people with CF, one of the most commonly used questionnaires is the HADS [50, 204, 207, 208]. While the HADS is not specific to CF, it has been developed for use in people with chronic medical conditions [204], and has been previously used in the CF population [50, 209, 210]. The HADS is a multi-item questionnaire which takes less than 5 minutes to complete. This questionnaire encompasses 14 statements related to anxiety and depression, with higher scores representing greater feelings of anxiety and/or depression, and a score of ≥11 used to indicate the person requires follow-up assessments for possible clinical anxiety and/or depression [211]. A four-point Likert scale (0 to 3) is used to respond to each question, with the sum of raw scores categorising people into 'mild', 'moderate' and 'severe' groups. The reliability of the HADS is acceptable for both the anxiety and depression domains (HADS-Anxiety scale: Cronbach $\alpha = 0.8$; HADS-Depression scale: $\alpha = 0.8$) [212].

Part 3

Part 3 of the literature review discusses the usual treatment regimen for a person with CF, separated into pharmacological and non-pharmacological treatment components.

2.3 Treatment and burden of disease

There is consensus across international guidelines that people with CF are likely to receive optimal care when they are managed by a specialist CF centre (where available), which includes regular contact (i.e. quarterly) with a multidisciplinary team [97]. In Australia, a

typical CF clinic appointment includes review of respiratory function (i.e. undertaking spirometry); review of medication and symptoms by a physician with specialist training in the management of CF; review of physiotherapy treatment that includes exercise training, inhalation therapy and airway clearance techniques [4]; and discussion with a dietician regarding nutritional support and maintenance of weight. A CF multidisciplinary clinic appointment may also include discussions about optimisation of the pharmacological treatment with a pharmacist, social issues with a social worker, and mood and chronic disease coping strategies with a psychologist. Treatment of CF is undertaken on a daily basis, and during a respiratory exacerbation, it is recommended that physiotherapy treatment be performed twice-daily [4]. Further, early recognition of increased symptoms (that may indicate a respiratory exacerbation) and early initiation of treatment for respiratory exacerbation are considered important to minimise permanent damage to the respiratory system, maintain HRQoL and also to optimise survival [136, 213, 214]. The following sections provide an outline of the pharmacological and non-pharmacological treatments that people with CF endure on a daily basis. There may be some treatments which fall into both categories, for example, some forms of inhalation therapy (hypertonic saline); these have been reviewed in the non-pharmacological section due to their association with airway clearance treatment. In addition, while a number of treatment options outlined are not relevant to the studies undertaken as part of this program of research, the aim of this section is to highlight the high daily treatment burden that people with CF face and the need to consider methods to reduce the treatment time, complexity and overall burden for this population.

2.3.1 Pharmacological treatment

The chronic use of oral antibiotics, such as azithromycin for *P. aeruginosa*, may be part of the usual treatment regimen for people with CF [215, 216]. For anti-infection treatment during an exacerbation, antibiotics may be administered intravenously rather than orally [215]. Early treatment with antibiotics is vital in the event of a respiratory exacerbation [215, 217]. In 2015, almost 94% of people with CF in the USA were prescribed antibiotic therapy for an exacerbation, via nebulisation, orally or intravenously [104]. In Australia, according to the Australian Cystic Fibrosis Data Registry, 64% of people with CF were prescribed any type of antibiotic for an exacerbation in 2015, though this figure may be an underrepresentation due to missing data in the registry [92]. Despite a large proportion of people with CF being treated with antibiotics for respiratory function decline, the quality of the evidence in this area is poor and relies largely on clinical experience [218]. The optimal duration of antibiotic treatment during an exacerbation therefore remains unknown but may

vary from 14 to 21 days [218]. In a recent Cochrane systematic review by Plummer et al. [219], no eligible studies were identified that investigated the optimal timeframe for antibiotic therapy [219]. Following an exacerbation, 25% of people with CF do not return to their 'pre-exacerbation' respiratory function, despite what is considered 'optimal' antibiotic treatment; this may be related to the development of a bacterial resistance to treatment [136]. Therefore, the duration of antibiotic treatment is individualised based on patients' clinical response to therapy [219]. Additionally, the CF guidelines for treatment of respiratory exacerbations recommended that the type of antibiotic be based on susceptibility testing [220].

Three studies of 354 participants support the prescription of low-dose oral corticosteroids to manage the inflammatory response in people with CF [221]. However, data on the benefits and associated risk of long-term corticosteroid use in people with CF has not been meta-analysed due to the low number of studies in this area (n = 3).

The high viscosity of sputum in people with CF is in part related to the high presence of deoxyribonucleic acid (DNA) from neutrophils that are present within the airway. The enzyme dornase alpha (Pulmozyme®), a recombinant human deoxyribonuclease, reduces the viscosity of sputum in the respiratory system, irrespective of disease severity [222-225]. Dornase alpha degrades free DNA that collects in sputum. Degradation of the DNA reduces the viscosity of sputum and assists the ease of airway clearance techniques. Long-term use of dornase alpha improves respiratory function and reduces the rate of respiratory exacerbations in people with CF [226]. Traditionally, people with CF are advised to administer this nebuliser medication 30 minutes before performing airway clearance techniques, the rationale being that 30 minutes is required for the medication to take effect and reduce the viscosity of sputum. However, inhaling dornase alpha following airway clearance techniques is equally as effective, as the drug can be deposited in peripheral areas of the respiratory system, which may not have been possible prior to airway clearance. These findings are highlighted in two Cochrane systematic reviews and meta-analyses by Dentice and Elkins [224, 227] of five studies (n = 122 participants). Irrespective of whether this medication is taken before or after airway clearance, dornase alpha disrupts sputum for 8 hours and therefore long-term daily maintenance of this treatment is recommended. In people with mild and moderate disease, dornase alpha should be administered a minimum of once per day. In people with more severe disease, twice-daily inhalation is recommended [227]. In addition, the continuation of dornase alpha throughout a period of exacerbation is recommended [215].

Modulators such as lumafactor and ivacaftor are medications that involve modifying the underlying defect within the *CFTR* gene [228]. While lumacaftor corrects the misprocessing within the *CFTR* gene, ivacaftor increases the CFTR channel opening time, which can normalise Cl^- transport across the cell membrane [229]. In 2017, the CF Foundation developed a set of guidelines including 30 recommendations for the use of modulators in people with CF [229]. These guidelines were developed by conducting a systematic review and evaluating the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, in conjunction with expert and consumer consensus. For people with CF aged ≥12 years with a homozygous *F508del* mutation, the chronic use of lumacaftor (a 'corrector') and ivacaftor (a 'potentiator') has been recommended. The chronic use of ivacaftor is recommended for people with *G551D* mutation [229]. High-quality evidence suggests that ivacaftor can improve respiratory function and HRQoL, and reduce the rate of respiratory exacerbations [225]. Recent guidelines also support the use of gene-modifying medications in a wider group of people with CF, for example, people with alternative *CFTR* mutations [229]. More recently, tezacaftor, a CFTR 'corrector', has been developed as a potential alternative for people with CF who are homozygous for the *Phe508del* mutation [230] or heterozygous for the *G551D/Phe508del* mutations [231]. While gene modification therapy, including triple therapy, is a vital component of CF treatment for people with the appropriate *CFTR* mutations, current research is directed to making these gene-modifying medications available for all people with CF, irrespective of their *CFTR* mutation and country of residence. It is acknowledged that these triple therapy medications will soon be seen in several countries, which will have a dramatic impact on life expectancy for people with CF.

Extensive review of current treatment for CFRD is largely outside of the scope of this literature review. For completeness, insulin therapy is recommended for people with CF who are insulin insufficient to optimise weight, respiratory function and survival [112].

2.3.2 Non-pharmacological treatment

2.3.2.1 Exercise

The precise mode and intensity of exercise, and length of exercise training required to obtain a benefit in exercise capacity, HRQoL and other important clinical outcomes in people with CF has not been established [37, 232]. However, current national clinical practice guidelines recommend that people with CF perform 30 to 60 minutes of aerobic exercise daily throughout their life, a recommendation that is consistent with guidelines provided for the general population [4]. The evidence on exercise in people with CF will be discussed further

in Section 2.4. Despite the benefits of exercise training and maintaining a physically active lifestyle, these daily exercise recommendations may not be possible in people with CF who, consistent with the general population, have competing demands on their time such as work, study and family, but also have a high daily treatment burden. In a study by White and colleagues [54] in 57 adults with CF (aged 26 ± 7 years), almost 70% of participants reported that 'lack of time' and 'feeling too tired' were the main barriers to completing the recommended daily exercise training. However, in a recent study investigating the relationship between activity and fatigue in adults with CF (median age 33 years, FEV_1 64% predicted), higher levels of physical activity were found to be associated with reduced general fatigue ($\beta = -0.7$, $p = 0.03$) and reduced physical fatigue ($\beta = -0.6$, $p = 0.09$). Physical activity and exercise training may therefore be an effective method to manage fatigue levels in this population [203]. In order to mitigate the impact of exercise training on the currently high daily treatment burden, an alternative training approach, such as HIIT, may be a more efficient option to optimise exercise capacity (discussed in Section 2.5).

2.3.2.2 Inhalation and airway clearance techniques

Irrespective of age and disease severity, airway clearance techniques are a cornerstone of daily CF treatment [4, 233, 234]. Undertaking regular airway clearance aims to prevent sputum plugging in the lungs, inflammation, respiratory infection and the development of bronchiectasis. Commonly utilised techniques include active cycle of breathing technique (ACBT), autogenic draining, positive expiratory pressure (PEP) with and without oscillation, exercise with forced expiratory techniques, and assisted and positional techniques (i.e. percussions, vibrations and postural drainage) [235]. No airway clearance technique appears to be superior to another. Therefore, guidelines recommend that techniques are prescribed based on patient preference and individual effectiveness [4, 233-237]. 'Active' techniques such as ACBT and PEP should be considered the first line of treatment. 'Assisted' techniques, such as percussions and vibrations (repetitive 'clapping' or 'shaking' of the chest wall), require a therapist or additional person to complete and, therefore, are only recommended if a person is unable to undertake active techniques [236]. In-depth review of each airway clearance technique is beyond the scope of this chapter.

Dehydration of exocrine glands due to a mutation of the *CFTR* gene has been previous described. Rehydration of the respiratory system is possible with the use of various nebulised treatments, which improve the effectiveness and ease of airway clearance. While inhalation therapies are a 'pharmacological' treatment, they have been included in this section as many are commonly administered prior to, during or following airway clearance techniques [4, 233, 234, 237]. The most common inhaled hydrating agent is hypertonic saline. Hypertonic

saline is an osmotic stimulus that rehydrates sputum in the respiratory system and decreases the likelihood of contracting *P. aeruginosa*. Although it is possible to dilute the concentration of hypertonic saline according to patient tolerance [234], ideally the full concentration of hypertonic saline (between 6 and 7%) should be prescribed if tolerated [238, 239]. Undertaking regular inhalation of hypertonic saline may improve respiratory function and reduce the frequency of respiratory exacerbations [239]. Use of hypertonic saline throughout an exacerbation is considered safe and effective to optimise airway clearance [240]. Clinically, people with CF may prefer to complete airway clearance techniques in combination with inhalation therapy. Evidence regarding completing airway clearance techniques and inhalation therapy (i.e. hypertonic saline) concurrently is conflicting. While combining the two therapies reduces the treatment time burden, the combination may also reduce the size of the nebulised particles and particle deposition in the peripheral airways [4].

Guidelines support the continuation of airway clearance techniques (with a potential increase in treatment frequency) and inhalation therapies during a pulmonary exacerbation [215]. In the case of severe exacerbation, non-invasive ventilation may be required to support airway clearance [215].

2.3.2.3 Nutritional treatment

The nutritional status of people with CF is an important clinical factor due to its association with respiratory function and survival [97, 241]. A large observational study of 3,142 participants found that, from as early as 4 years of age, greater weight was associated with better respiratory function by adulthood (i.e. 18 years) [242]. In a smaller retrospective analysis, this positive association between weight and respiratory function was shown to persist into the second and third decade of life (r^2: 0.3 [FEV_1 at 20 years] and 0.3 [FEV_1 at 30 years]) [243]. Poor nutrition can be due to chronic malabsorption. In addition to the increased work of breathing and decreased appetite during an exacerbation, daily exercise training recommendations may further increase weight loss in this population. Poor nutrition or 'failure to thrive' is less prevalent now than in the past. The reason for improvements in overall nutrition of people with CF may be related to improved nutritional awareness and, more recently, gene-modifying medications. In a longitudinal cohort study completed by Stephenson et al. [96] in Canada from 1990 to 2012, 19% of people with CF (n = 5,787) had a body mass index (BMI) < 19 $kg \cdot m^{-2}$, compared to 31% of people in the 1990s. Notwithstanding recent medical advancements, malnutrition and low body mass remain potentially life-limiting problems for people with CF. Papalexopoulou et al. [244] demonstrated that lower fat-free mass is associated with lower respiratory function (r = 0.4,

$p = 0.02$), respiratory muscle function ($r = 0.5$, $p = 0.01$) and exercise tolerance ($r = 0.7$, $p < 0.001$). Therefore, nutritional management remains a highly important treatment goal in this population.

Optimisation and maintenance of weight through the consumption of adequate nutrition is an important aspect of daily treatment for people with CF across the lifespan [387]. Specifically, a diet with high protein, salt, fat and calorie count, and pancreatic replacement therapy is recommended to optimise nutrition. A recent Cochrane systematic review by Smyth and Rayner [241] involving three studies identified that nutritional support in the form of oral supplement drinks (i.e. juice or shakes) does not improve nutritional status in people with CF and should not be provided as an 'essential' long-term treatment component. Rather, short-term use of oral caloric supplementation may be used to support nutritional intake (e.g. during a respiratory exacerbation when appetite is low), and advice regarding a CF-appropriate diet is more useful in the long term [241].

2.3.3 Treatment burden, complexity and adherence

The previous sections highlight the complexity of daily treatment faced by people with CF. While pharmacological and non-pharmacological treatments slow the progression of respiratory disease and have improved the life expectancy of people with CF in recent decades, the treatments are time consuming. Many treatments need to be repeated throughout the day and require self-management across the lifespan. The average number of treatments for people with CF is seven [47], which can take 2 to 4 hours per day to complete [47]. The treatment time burden is likely considerably higher than in other chronic respiratory conditions, such as asthma [245] and bronchiectasis [246, 247], which is likely due to the multi-organ nature of the disease (i.e. all exocrine glands). The time burden and complexity of treatment is represented in Figure 2.1.

Adding to this time burden is the complexity of daily treatment for people with CF [47]. Treatment complexity increases over the lifespan and is the greatest among adults with CF and those with more severe respiratory disease [248]. In a large multicentre study of 7,252 people with CF, data were collected on treatment regimens over a 3-year period. Treatment complexity was assessed using the Treatment Complexity Score and assigned a value of 1 (least complex) to 3 (most complex). Treatments such as tablets and inhalers were deemed to be the least complex treatments, nebulised therapies and pancreatic enzymes were regarded as moderately complex, and airway clearance techniques, insulin and the administration of non-invasive ventilation or supplemental oxygen in the later stages of the disease were regarded as the most complex treatments [248]. The complexity of treatment

increases with increasing age and may be associated with levels of adherence; that is, adherence to treatment is higher in children (due to lower complexity of treatment and, probably, because their treatment regimens are often managed by a parent or guardian), and lower in adolescence and adulthood [248].

The term adherence has been defined as the extent to which a person's behaviour (e.g. taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider [249]. In a systematic review of 26 studies in people with CF, adherence to treatment was reported as variable [250]. Adherence to pancreatic enzyme replacement therapy ranged from 27 to 97% and medication use from 32 to 85%. Adherence to nutritional supplementation ranged from 22 to 98%, to exercise from 57 to 88%, and to airway clearance techniques from 33 to 91%. The reasons for variability in adherence to different treatments remain poorly understood [251], but is likely to be influenced by patient knowledge, psychological acceptance or resistance, and level of education regarding adherence throughout childhood [252]. Other factors that can influence adherence include lack of time, side-effects of treatment, associated treatment costs and the complexity of certain treatments [253].

Adherence to certain treatments, for example medication, may predict future respiratory exacerbations. In a longitudinal retrospective review of 95 people with CF, pharmacy records were used to determine the medication possession ratio (sum of days medication supply was received divided by the number of days the medication was prescribed). Lower medication possession ratio was a predictor for having a respiratory exacerbation. When controlling for sex, treatment complexity and respiratory function, a strong association was found between the medication possession ratio and the requirement for intravenous antibiotics to treat a respiratory exacerbation over a 12-month period (incidence rate ratio 2.3, $p = 0.05$) [254]. Additionally, poor adherence to treatment has been associated with poorer mood ($r = -0.4$, $p < 0.001$) [255, 256].

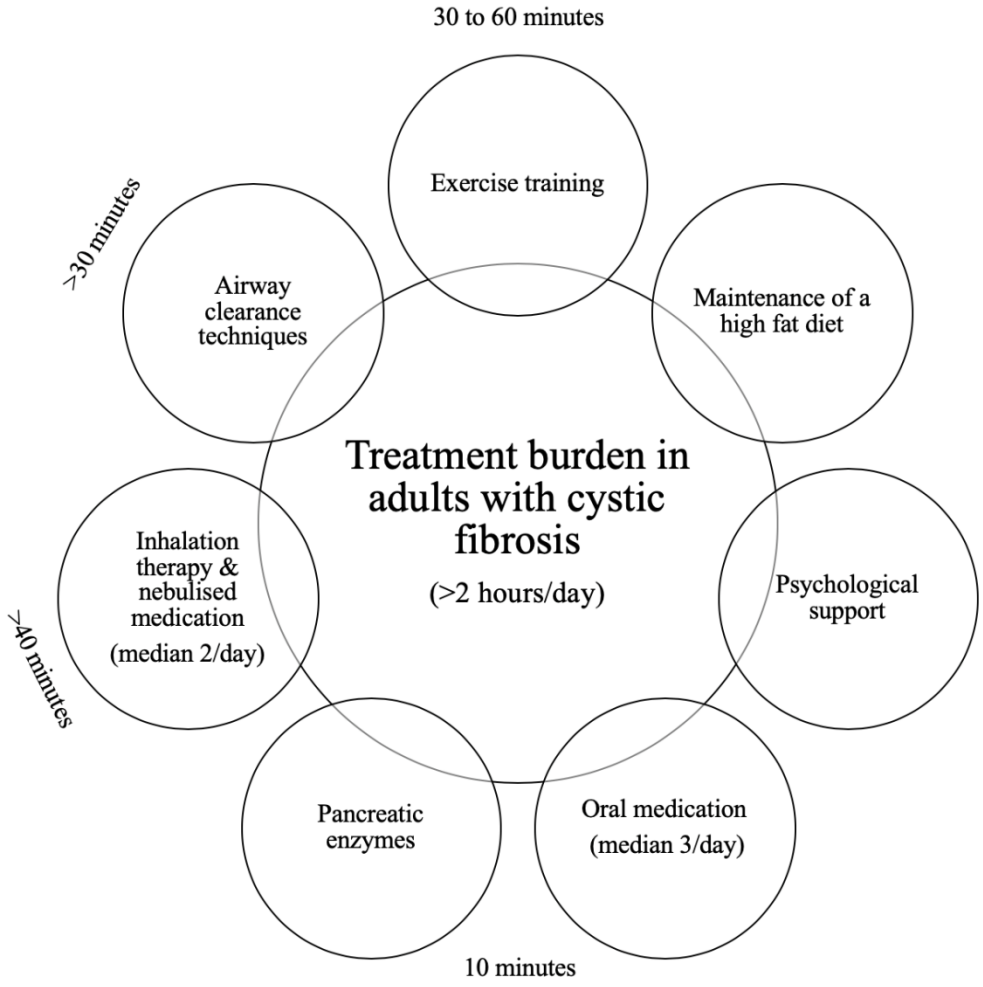


Figure 2.1 Treatment burden in people with cystic fibrosis

Note: Data from two studies were used to create this figure [47, 248]. Where data were available, median amounts and estimated treatment times have been included for treatments estimated to take > 10 minutes.

Part 4

The final part of this literature review explores the evidence for exercise training in people with CF, with a focus on aerobic exercise, in particular HIIT.

2.4 Evidence for exercise training

In people with CF, higher exercise capacity has been positively associated with better HRQoL [257, 258], lower levels of fatigue [203], better sleep quality [259], lower risk of hospitalisation [260] and improved glycaemic control in people with CRFD [112]. Furthermore, people with CF who have higher exercise capacity (measured as VO_{2peak}) are also characterised by a slower rate of decline in FEV_1 [261], thereby prolonging survival and/or delaying the need for lung transplantation [19, 20, 38]. Kaplan–Meier survival curves for people with CF grouped according to measures of VO_{2peak}, reported in a recent study by Hebestreit and colleagues [38], can be found in Figure 2.2.

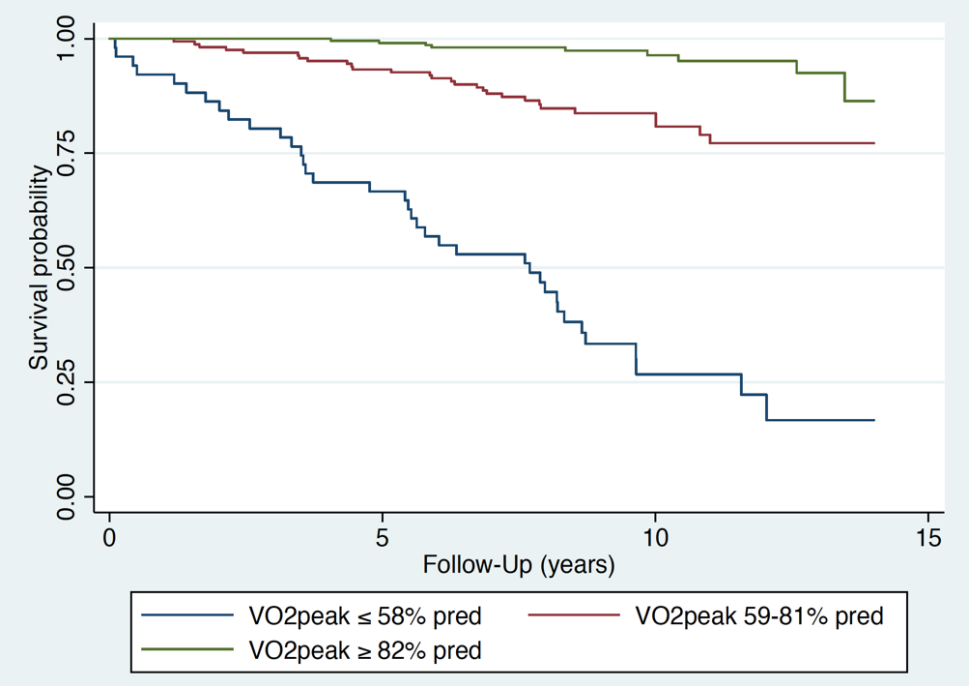


Figure 2.2 Kaplan–Meier survival curves for people grouped according to their VO_{2peak}

Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Hebestreit H et al. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J Respir Crit Care Med. 2018 [38]. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. Abbreviations: VO_{2peak}: peak rate of oxygen uptake.

Exercise training is defined as participation in a structured program of regular moderate-to-vigorous intensity physical activity designed to improve physical performance, cardiovascular function, muscle strength, or a combination of these [262]. Data from RCTs in people with CF show that implementing an exercise training program improves outcomes such as exercise capacity and HRQoL [263-267] (see Section 2.2). In addition to improving exercise capacity and HRQoL, exercise may have a protective role against developing feelings of anxiety and/or depression [206], and may facilitate sputum removal, improve glycaemic control for people with CFRD and reduce the risk of developing osteoporosis [37]. Previous work supports the implementation of 'supervised' exercise training programs over unsupervised programs [265, 268, 269]; however, both strategies can facilitate improvements in various markers of exercise capacity [268]. In addition, in clinical rehabilitation, the term 'supervision' has traditionally been used to depict interventions whereby a therapist is present for the duration of the session. However, the specific techniques employed throughout the supervised session to change the behaviour involved are seldom reported in detail [270]. As such, the ability to replicate the supervision component of the intervention is limited. Further detail on behaviour change techniques is available in Chapter 7.

There are some data to suggest that exercise training can optimise and maintain participation in physical activity. People with CF who undertook a structured exercise program were found to spend more time (hours per week) doing vigorous physical activity, when measured objectively via accelerometry, up to 2 years following an exercise training program, compared to people who did not undertake a structured exercise program (between-group difference in change score from baseline to 2 years following intervention: 1.6 ± 0.8 hours per week) [271].

2.4.1 Aerobic exercise training

Aerobic exercise is defined as continuous, repetitive movement, using large skeletal muscles, that results in an increase in cardiovascular and ventilatory demand [43, 272]. Examples of aerobic exercise include walking, running, cycling and swimming. Most exercise studies in people with CF focus on 'traditional' aerobic exercise training, that is, continuous exercise undertaken at a moderate intensity. This type of training is usually undertaken at approximately 60 to 80% of the VO_{2peak} or 70 to 85% of the maximum HR [268] [4]. A summary of RCTs investigating the effectiveness of exercise training on various outcomes in people with CF is available in Table 2.1.

The most recent Cochrane systematic review on exercise training for people with CF included data from 13 studies and a total of 402 participants. These studies were of low to moderate methodological quality, affected most commonly by performance and selection bias [37]. Data on aerobic exercise training in people with CF are mostly limited to children, or a combination of children and adults [37]. For example, an RCT conducted by Selvadurai and colleagues [265] allocated children with CF (aged 13 ± 2 years, FEV_1 57 ± 18% predicted) to either an aerobic exercise training group (n = 22), a resistance training group (n = 22) or a control group (n = 22). At the completion of the intervention period (approximately 3 weeks), those allocated to the aerobic exercise training group demonstrated a 22% improvement in exercise capacity, which was greater than any change seen in the resistance training group or control group. Likewise, in a study of children living with CF (aged 14 ± 1 years, FEV_1 75 ± 21% predicted), when compared with a control group, 12 weeks of exercise training was shown to improve HRQoL related to physical function, measured using the CFQ-R disease-specific HRQoL questionnaire (between-group MD 14 points, 95% CI 10 to 18) [264].

Of the studies included in the systematic review [37], only one was undertaken in adults [266]. Specifically, Moorcroft and colleagues [266] undertook an RCT investigating the effects of individualised exercise training in adults with CF (aged 24 ± 6 years, FEV_1 2 ± 1 L) over 1 year. Being an individualised intervention, participants played an active role in prescribing the intervention, with a focus on aerobic and resistance modes of exercise. For example, participants were permitted to choose general aerobic exercises such as walking, jogging, cycling, swimming or participation in a sport, as well as resistance exercises. The programs were individualised, though each lasted for approximately 20 minutes, as well as a warm-up and cool-down. The constant work rate test was undertaken at a workload of 40% and then 55% of W_{peak}, using both arm and cycle ergometry. Following the intervention, mean blood lactate levels taken at the end of a constant work rate test differed between the intervention and control groups (MD −0.8 mmol/L, 95% CI −1.5 to −0.1). Although participants were asked to record their adherence to the program using a diary, these data were not reported. Further, the program was both individualised and unsupervised (except for monthly review appointments with the physiotherapist) and, therefore, it was not possible to decipher which particular mode, intensity or frequency of exercise was likely to be most effective.

While the optimal method of exercise training in people with CF requires further investigation [37], there are a number of potential limitations to prescribing moderate intensity continuous aerobic exercise for people with CF. First, this type of training requires

a significant time commitment of at least 30 minutes per day in adults, or 60 minutes per day in children and adolescents with CF [4]. Furthermore, some forms of moderate intensity continuous exercise may elicit substantial oxygen desaturation (i.e. > 4% from baseline) [60]. In addition, a small study of 12 children with CF (aged 15 ± 2 years, FEV_1 90 ± 22% predicted) demonstrated an increased concentration of circulating biomarkers for inflammation following an acute bout of moderate intensity continuous exercise compared to HIIT [273]. Finally, moderate intensity continuous exercise may be perceived as less enjoyable than other forms of exercise training such as HIIT [58].

Table 2.1 Description of randomised controlled trials investigating effects of exercise training on measures of exercise capacity in people with cystic fibrosis

	Participants and design			Training protocol		Results
Study	**Number/age group**	**Inclusion criteria**	**Type of exercise**	**Intensity**	**Frequency and duration**	**Between-group difference**
Hebestreit [271] 2010	n = 38 (paediatric and adult)	Confirmed diagnosis of CF ≥12 years of age FEV_1 ≥35% predicted Capacity to perform physical activity	Intervention: advice to increase physical activity; endurance or combined training (endurance and resistance) Control: asked to maintain a constant level of physical activity	Below gas exchange threshold (equivalent heart rate)	Intervention: 3 times per week for 30 to 45 minutes for the first 6 months of the study	ΔVO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$): MD 3.7, 95% CI 2.9 to 4.6 ΔW_{peak} ($W \cdot kg^{-1}$) MD: 0.37, 95% CI 0.3 to 0.4
Klijn [264] 2004	n = 23 (children)	Stable in the preceding 3 months FEV_1 > 30% predicted	Intervention: anaerobic training (20- to 30-second bursts); therapist present Control: asked not to change usual routine	Link provided for supplementary material not functional. Unable to determine intensity of exercise.	2 times per week for 12 weeks	ΔVO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$): MD 2.1, 95% CI 0.0 to 4.3 ΔW_{peak} (W) MD: 13, 95% CI 3 to 23

Schneiderman-Walker [269] 2000	n = 65 (children)	Not provided	Intervention: participation in preferred aerobic activity, one counselling session Control: asked to maintain usual level of physical activity	5-minute warm-up and cool-down. Target heart rate of 70 to 80% of peak.	20 minutes per session, 3 times per week for 3 years	Slower decline in lung function over 3-year study period. Exercise capacity measures not reported at follow-up.
Selvadurai [265] 2002	n = 66 (children)	Diagnosis of CF Admitted to hospital for treatment of a respiratory exacerbation	Intervention (1): aerobic training – 30 minutes per day (running or cycling) Intervention (2): upper and lower limb resistance training (5 x 10 sets) Control: asked not to alter level of activity	Intervention (1): 70% peak heart rate Intervention (2): 70% of the maximal subjectively reported resistance	1 week	ΔVO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$): MD 6.7, 95% CI 3.6 to 9.7 (between both intervention groups)

Moorcroft [266] 2004	n = 51 (adults)	Attending CF clinic Confirmed documentation of CF	Intervention: upper and lower body exercise (individual preference) Control: no change	Based on fitness and disease severity (initial assessment). Perceived intensity used to guide aerobic intensity. Starting weight for resistance exercise was one that could be lifted 10–15 times, progressing to 20–30 times, then weight increased.	Approx. 20 minutes per session. Aim for 3 sessions of upper and lower body exercise per week for 1 year	Δ blood lactate ($mmol \cdot L^{-1}$): MD −0.8, 95% CI −1.5 to −0.1
Rovedder [274] 2014	n = 41 (adults)	Diagnosis of CF Aged ≥16 years Clinically stable	Intervention: provided with a specific home exercise program (aerobic and resistance) with support material and practical demonstration Control: standard care	Not specified	Daily for 3 months	No laboratory-based exercise tests undertaken. Δ6MWD: no between-group changes

Abbreviations: 6MWD: 6-minute walk distance, CF: cystic fibrosis, CI: confidence interval, FEV_1: forced expiratory volume in 1 second, MD: mean difference, VO_{2peak}: peak rate of oxygen uptake, W: Watts, W_{peak}: peak work rate. There is little data on the minimal clinically important difference (MCID) for VO_{2peak} in people with CF. In people with chronic obstructive pulmonary disease, despite little data, the MCID has been suggested as a change of $\sim 0.04 \pm 0.01$ $L \cdot min^{-1}$ or 10 W. The MCID in 6MWD has been suggested to be between 25 and 33 m [42].

2.4.2 Resistance training

Resistance training is defined as physical training that improves muscular strength or endurance. While this type of training is less effective than aerobic exercise in changing VO_{2peak}, it can be used in addition to aerobic training to improve strength, fat-free mass and physical function [12]. In people with CF, there is a dearth of work exploring the effects of resistance training in isolation from aerobic exercise. Rather, studies tend to incorporate a combination of aerobic and resistance training, the former of which has been discussed previously (Section 2.4.1). In one RCT [274], participants (n = 41, aged 25 ± 8 years, FEV_1 58 ± 25% predicted) were randomly allocated to complete a home exercise program, consisting of both aerobic and resistance training (n = 19), or to continue with usual care (n = 22), which included a review of current exercise guidelines and no formal exercise training intervention. On completion of the intervention period, the participants who completed the program demonstrated improvements in upper limb muscle strength (repetition maximum; RM) compared to the control group (MD 1.4, 95% CI 0.3 to 2.5). However, resistance training was not the sole focus of the intervention offered in the study and, therefore, it is difficult to confidently attribute this change to the implementation of resistance exercise. In addition, despite the program incorporating both upper and lower limb resistance exercises, there were no between-group changes in lower limb muscle strength following the training program. This may be associated with a lack of direct supervision and face-to-face encouragement (and reassurance) to increase the intensity as able. Participants received an initial assessment with a therapist to set their exercise program, which included a physical demonstration and printed instructions, as well as ongoing phone contact throughout the 3-month period. However, it is unclear whether or how the intensity of resistance exercises was progressed, or the level of adherence to the training program.

Another study conducted in adults with CF (aged 24 to 41 years, FEV_1 51 to 87% predicted) investigated the effects of a 12-week resistance (and aerobic) training program (n = 8) completed thrice-weekly, in comparison to a control group (n = 6) [275]. The resistance training program involved the upper and lower limbs, with 8 to 12 repetitions per exercise at a weight of 30 to 50% of the 1RM and a 60-second rest period between exercises. This resistance program was supplemented with 20 to 40 minutes of aerobic exercise (walking, jogging, cycling and/or elliptical training), which commenced at an intensity of 60% of the VO_{2peak} during weeks 1 to 4, and progressed by 10% each month thereafter. A therapist was present during the intervention intermittently (once per month). This study demonstrated a between-group difference in the magnitude of change in plasma glucose levels (MD 6.7 mmol L^{-1}, 95% CI 5.1 to 8.2). In addition, there were within-group improvements in

some elements of strength (e.g. leg press [+33 kg] and bench press [+7 kg]). However, these did not correspond with a between-group improvement in these outcomes favouring the exercise group. There were no changes in other outcomes, such as exercise capacity (VO_{2peak}) and respiratory efficiency (VE/VO_{2peak}), respiratory function (FEV_1 or forced vital capacity [FVC]), body composition (weight, BMI, body fat or fat-free mass), HRQoL, or objectively measured level of physical activity. This study did not reach the projected sample size (18 to 24 participants) so it is likely that the study was underpowered to detect differences in many outcomes [37, 275].

The effects of resistance training in people with CF during periods of hospitalisation is also unclear. One RCT undertaken in children with CF who were admitted to a hospital ward for treatment of an acute respiratory exacerbation (n = 66) allocated participants to a group who did aerobic training, a group who did resistance training or a control group [265]. The aerobic training involved 30-minute sessions comprising running on a treadmill or cycling at 70% of the HR_{max}. The resistance training involved upper and lower limb resistance exercises using gymnasium machinery, conducted at approximately 70% of the subjectively reported RM. Measurements were taken of body mass, fat-free mass and exercise capacity (VO_{2peak}) measured on a treadmill. Participants who completed a period of resistance training with a therapist present had greater weight gain, defined by the change in body mass at discharge compared to measurements taken at the start of the hospitalisation (3 ± 1 kg for the resistance training group compared to 0.1 ± 1 kg for the aerobic training group and 1 ± 1 kg for the control group). In addition, fat-free mass improved in the group who undertook resistance training (2 ± 1 kg for the resistance training group compared to 1 ± 0 kg for the aerobic training group and 1 ± 0 kg for the control group). There was a between-group difference in fat-free mass between the two exercise groups (MD 3, 95% CI 2 to 4), as well as between the resistance and control group (MD 2, 95% CI 1 to 3). Leg strength also improved for the resistance training group (18 ± 7 nanometre) but not for the aerobic training or control groups. These results are important in people with CF who commonly have difficulty gaining and maintaining weight due to the extrapulmonary disease process, but are also negatively affected by hospitalisation which may influence peripheral muscle weakness [276]. However, VO_{2peak} was lower in the resistance training group than in children who undertook aerobic exercise training. With greater VO_{2peak} being associated with longevity in this population, the findings of this study highlight the need for daily aerobic exercise training as part of usual care for people with CF [265]. Additionally, this study was completed in an inpatient setting with participants who were acutely unwell and thus the applicability of these results in an outpatient setting remains unclear.

With 30 to 60 minutes of daily aerobic exercise currently recommended, it can be difficult for people with CF to factor in time for both aerobic and resistance training. In the first instance, investigation into a more time-efficient approach to exercise training, such as HIIT, is warranted in this population. Given that people with CF commonly present with impaired muscle strength and malnutrition, is seems reasonable to supplement an aerobic training program with resistance training.

Respiratory muscle training is acknowledged as a form of resistance training for people with CF. However, further evaluation of this intervention is outside of the scope of this literature review.

Part 5

2.5 High intensity interval training

This section comprises an invited narrative review investigating the effects of HIIT on exercise capacity in adults with chronic respiratory conditions, including CF. This invited review was published in *BMC Sports Science, Medicine and Rehabilitation* in March 2020 [87]. It defines HIIT and explains why this approach may be useful in people with chronic respiratory conditions.

Exercise training is important in the management of adults with chronic respiratory conditions. Systematic reviews, undertaken in clinical populations, such as adults with COPD [1, 2], CF [3, 4], non-CF bronchiectasis, interstitial lung diseases (ILDs) [5-7], asthma [8] and non-small cell lung cancer (NSCLC) [10, 277, 278], have shown that exercise training is effective at increasing components of cardiorespiratory fitness (i.e. the peak rate of oxygen uptake; VO_{2peak}) and exercise capacity (i.e. the peak work rate; W_{peak}). Additionally, exercise training has been demonstrated to reduce the severity of symptoms experienced during daily life, such as dyspnoea and fatigue, and improve HRQoL [11]. In the general population, exercising at moderate- to high- intensity is recommended to optimise the magnitude of improvement in exercise capacity [12]. Consistent with these data, studies of people with COPD suggest that, in contrast with low-intensity exercise, high intensity exercise training may be advantageous in terms of eliciting a physiological training response [13-16]. These data are in keeping with the overload principle, which states that in order to improve cardiorespiratory fitness and/or exercise capacity, exercise training must be undertaken at an intensity that is greater than the load borne during daily life [18].

Regarding the mechanisms underpinning the improvements in cardiorespiratory fitness and/or exercise capacity, gains are not mediated through improvements in lung function [19-21]. In fact, some of the earliest work done in the area of exercise training for people with COPD [22] was met with scepticism as the gains in exercise capacity were demonstrated without any change in FEV_1. In the mid-1990s, seminal work demonstrated that the changes in exercise capacity were mediated, at least in part, by improved condition of the peripheral muscles, largely the vastus lateralis [23]. For example, cycle ergometry training resulted in increased activity of two oxidative enzymes, citrate synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HADH) (from 22 ± 4 to 26 ± 4 $\mu mol \cdot min^{-1} \cdot g^{-1}$ muscle for CS, $p < 0.05$, and from 6 ± 3 to 8 ± 3 $\mu mol \cdot min^{-1} \cdot g^{-1}$ for HADH, $p < 0.01$) [23]. In populations characterised by chronic respiratory conditions, high intensity exercise training may also optimise cardiovascular health [279-281]. Although these data exist predominantly for people with COPD, guidelines regarding the prescription of exercise training for people with other chronic respiratory conditions often recommend training at moderate intensity or higher [4, 24, 25]. However, achieving high intensity exercise may be challenging for this clinical population. The reasons for this are multi-factorial. First, people with moderate to severe disease are likely to demonstrate ventilatory limitation [13, 26], coupled with worsening respiratory mechanics during exercise [14], both of which serve to constrain the intensity that can be achieved before the onset of intolerable dyspnoea. Second, some people with chronic respiratory conditions, who do not qualify for long-term oxygen therapy, demonstrate a marked reduction in peripheral capillary oxygen saturation on exertion. This is due largely to ventilation and perfusion mismatch (V/Q mismatch) and is generally more pronounced in people with severe respiratory disease [27]. In some clinical populations, such as those with COPD who demonstrate transient exertional desaturation despite being normoxaemic at rest, recent data suggests that, when compared with gains derived from training on room air, the use of supplemental oxygen offers no additional benefit [28]. In other populations, such as those with ILDs, even high-dose supplemental oxygen may not be able to prevent marked desaturation [29, 30]. In the presence of transient exertional desaturation, clinicians may choose to reduce the exercise intensity, which compromises the training dose achieved. Third, many people with chronic respiratory conditions, particularly those who are older, have comorbidities which contribute to the difficulty of achieving high intensity exercise. These conditions may include osteoarthritis [31], feelings of anxiety and depression [32], or obesity [33]. Given these challenges, there has been an interest in applying interval-based training as a strategy to optimise the load that can be tolerated during exercise training [34-36].

2.5.1 High intensity interval training

Intermittent or interval training approaches are characterised by repeated cycles of work interrupted by rest [282, 283]. The main difference between these approaches is that, for intermittent training, the patient chooses the work and rest times based on the tolerability of their symptoms, whereas for interval training, the work to rest ratios are prescribed by the therapist. Both approaches are likely to be advantageous in people with severe respiratory disease, who, due to intolerable symptoms, may be unable to engage in continuous exercise at an intensity sufficient to induce a training adaptation. In this population, punctuating work periods with rest periods provides intermittent relief from the ventilatory demand associated with exercise, which serves to reduce the work of breathing and dyspnoea. This in turn offers the opportunity to optimise the training intensity that can be borne during the next work period [26]. Given this advantage, the work intervals are often performed at higher intensities than could be tolerated with continuous training. Repeating this work to rest cycle allows the prolonged exposure of the peripheral muscles to the stimulus necessary to elicit physiological adaptations [284]. In the literature, interval-based training has been described more often than intermittent training because, in contrast with an intermittent approach, interval-based training is highly standardised and reproducible, and the parameters can be manipulated by the therapist. As the work periods are performed at high intensities, this type of training is often described as high intensity interval training, or HIIT.

Studies that were reviewed needed to meet our definition of HIIT; specifically, the work intervals used during the training program were conducted at an intensity equivalent to ≥80% of peak (W_{peak}, peak power, VO_{2peak} or HR_{max}) determined during a baseline maximal laboratory-based exercise test, in which work rates progressively increased each minute. As the optimal work to rest ratio for HIIT is unknown, no criteria for inclusion in this review were set for this parameter. Nevertheless, it is worth noting that in order to maximise the stimulus needed to improve the oxidative capacity of the peripheral muscles, a ratio that maximises workload during the work periods and minimises the duration of the rest intervals would seem ideal. In this way, exposure of the peripheral muscles to the milieu of by-products associated with anaerobic metabolism could be maximised, a stimulus necessary to promote mitochondrial biogenesis [55, 284].

One study in people with COPD compared fluctuating work to rest intervals of 4 minutes of work to 4 minutes of rest, using a sinusoidal wave form, with the use of faster fluctuations, characterised by 1 minute of work to 1 minute of rest. Compared with the slower fluctuations, faster fluctuations between work and rest allowed people with COPD to achieve supramaximal work rates (i.e. 120% of their W_{peak}), with considerably less ventilatory load

[284]. This suggests that faster fluctuations between work and rest intervals may offer advantage over slower fluctuations for improvements in muscle adaptation, cardiorespiratory fitness and exercise capacity.

Another advantage of HIIT is its efficiency for producing training-related gains. Specifically, in sedentary healthy adults as well as in athletes, this type of exercise produces physiological evidence of a training effect over a period of as little as 2 weeks [55]. In healthy young adults (n = 8, mean ± SD, aged 22 ± 1 years, VO_{2peak} 45 ± 3 $mL \cdot kg^{-1} \cdot min^{-1}$), as few as six sessions of cycling-based HIIT over 2 weeks has been shown to produce a significant improvement in endurance capacity (12% change from baseline), and changes in the peripheral skeletal muscles (i.e. vastus lateralis) which were indicative of increased oxidative capacity. These changes were over and above any seen in a control group [285]. However, it is important to note that this study did not show improvements in cardiorespiratory fitness (VO_{2peak}), despite improvement in other exercise outcomes.

Importantly, a HIIT protocol may also be more time-efficient than a continuous protocol [286]. That is, an RCT undertaken in sedentary males (n = 25, aged 27 ± 8 years, BMI 26 ± 6 $kg \cdot m^{-2}$) allocated participants to one of three groups: (i) HIIT (n = 9), which comprised three bursts of 20-second cycle sprints interspersed with 2-minute periods of low-intensity cycling, completed three times a week for 12 weeks; (ii) continuous cycling (n = 10), which comprised 45 minutes of cycling at approximately 70% HR_{max}, completed three times a week for 12 weeks; or (iii) a control group (n = 6), which did not receive any cycling training. This RCT demonstrated that, compared with the control group, participants in both of the exercise groups increased their W_{peak} (HIIT: MD 62 W, 95% CI 4 to 120; continuous cycling: MD 58 W, 95% CI 7 to 109). However, despite the substantially shorter training time in the HIIT group compared with the continuous exercise training group (30 minutes a week compared to 135 minutes a week with workloads titrated according to rate of perceived exertion), the VO_{2peak} on completion of the exercise training period was similar between groups (MD −2 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI −10 to 6) [286]. The strong physiological rationale for HIIT coupled with data demonstrating both effectiveness and efficiency in sedentary populations makes this approach an attractive option for use in adults with a chronic respiratory condition. Further, in contrast with other approaches that aim to optimise the training load borne by the peripheral muscles by reducing the ventilatory load associated with exercise (e.g. proportional assist ventilation, heliox), interval training does not require extra equipment and is an inexpensive option that can be incorporated into daily life.

Recent work has indicated that HIIT is used in clinical practice. That is, our group recently conducted a survey of Australian and New Zealand CF centres to determine, in part, the extent and scope of exercise training in people with CF [162]. The results of this survey found that HIIT is commonly prescribed by therapists despite limited research to support this type of training. In addition, people with ILDs are often prescribed interval-based training as a 'lead-in' phase within studies investigating the effects of pulmonary rehabilitation in people with ILDs [287, 288].

The aim of this narrative review was to synthesise the data from studies that have reported the effects of land-based whole-body HIIT on cardiorespiratory fitness (VO_{2peak}) and/or exercise capacity (W_{peak}) in adults living with chronic pulmonary conditions, including people with COPD, CF, non-CF bronchiectasis, asthma, ILDs and NSCLC. This narrative review will provide an update of studies investigating whole-body HIIT in adults with COPD, and will be the first to review studies in other chronic pulmonary conditions. As HIIT is most often undertaken on a cycle ergometer in studies, outcomes reported on in this review were selected based on the principle of task specificity [289], and comprised VO_{2peak} and W_{peak} measured during a cycle-based cardiopulmonary exercise test. Where possible, for each condition, studies that have explored the effectiveness of HIIT compared to usual care (i.e. no exercise) are presented separately to those that have compared the effects of HIIT with continuous exercise training. This is the first review to take this approach.

2.5.2 Chronic obstructive pulmonary disease

Two studies have compared the use of HIIT, embedded within a 12-week pulmonary rehabilitation program, to no exercise (i.e. the comparison is a control group with no exercise or pulmonary rehabilitation program), on measures of exercise capacity in people with COPD [290, 291]. In one study, the HIIT intervention commenced with work intervals at 80% of the W_{peak}, interspersed with an active recovery (40% W_{peak}), for 30 and 90 seconds, respectively [290]. When compared with the usual care group (n = 15, aged 80 ± 6 years, FEV_1 60 ± 15% predicted), those who undertook HIIT (n = 14, aged 80 ± 8 years, FEV_1 47 ± 18% predicted) demonstrated greater changes in measures of cardiorespiratory fitness (VO_{2peak} MD 2 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 1 to 4) and exercise capacity (W_{peak} MD 16 W, 95% CI 5 to 27) [290]. In the other study, the HIIT intervention comprised a 45-minute session of 30-second intervals of 130 ± 18% W_{peak} interspersed with 30-second rest periods [291]. When compared with the usual care group (n = 43, aged 67 ± 8 years, FEV_1 45 ± 19% predicted), those who undertook HIIT (n = 85, aged 65 ± 8 years, FEV_1 49 ± 19% predicted) demonstrated greater changes in measures of exercise capacity, expressed as either VO_{2peak} (MD 2 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 1 to 4) or W_{peak} (MD 16 W,

95% CI 5 to 27) [291]. Nevertheless, as both studies explored the effect of HIIT provided within a pulmonary rehabilitation program, which included resistance exercises and education, the gains in exercise capacity cannot be directly attributed solely to the HIIT.

Several studies have compared the effect of HIIT with continuous training in people with COPD (Table 2.2). Data from these trials have been meta-analysed in previous reviews [35, 292]. However, we have found a further two trials since a previous comprehensive review and update that have compared the effect of HIIT with continuous exercise training on measures of exercise capacity in people with COPD [293, 294]. The findings of the previous comprehensive review demonstrated comparable effects of the two modes of exercise training on measures of cardiorespiratory fitness (VO_{2peak} MD 0.04 $L \cdot min^{-1}$, 95% CI 0.13 to 0.05) and exercise capacity (W_{peak} MD 1 W, 95% CI −1 to 3) [35]. Of the 10 studies that have compared HIIT with continuous training, three appeared to be of moderate quality [294-296], whereas the remaining seven studies were of fair to poor quality [26, 293, 297-301]. With the addition of the two new studies, the summary effect statistic suggests that, for both outcomes, there was no clear evidence for benefit of one form of exercise over the other (see Figure 2.3 and Figure 2.4, respectively). Of note, this result did not differ when studies were grouped according to whether or not the total amount of work between the HIIT group and a continuous group was matched [35], or when a random effects model was used.

Table 2.2 Description of studies comparing high intensity interval training with continuous exercise training in people with chronic obstructive pulmonary disease

	Study	Type of exercise	Interval exercise	Continuous exercise	Frequency and duration
Previous review [35]	*Arnardóttir [297] n = 60 2007	Cycling in people with COPD	≥80% peak power, followed by 30 to 40% peak power Duration: 39 minutes (intervals of 3 minutes:3 minutes)	≥65% peak power Duration: 39 minutes	2 x per week for 16 weeks
	Coppoolse [298] n = 21 1999	Cycling in people with COPD	90% peak power interspersed with 45% peak power, plus continuous cycling at 60% Duration: 30 minutes (intervals of 1 minute:2 minutes)	60% peak power Duration: 30 minutes	5 x per week for 8 weeks
	Mador [295] n = 41 2009	Cycling or treadmill in people with COPD	150% of continuous exercise target interspersed with 75% of target Duration: 20 to 40 minutes (intervals of 1 minute:2 minutes)	50% peak power and at 80% of 6MWT average speed Duration: 20 to 40 minutes	3 x per week for 8 weeks

	Nasis [299] n = 42 2009	Cycling in people with COPD	100% peak power and 45% peak power Duration: 30 to 40 minutes (intervals of 30 seconds)	60% peak power Duration: 30 to 40 minutes	3 x per week for 10 weeks
	* Puhan [296] n = 98 2006	Cycling in people with COPD	50% peak power of a steep-ramp test, followed by 10% peak power Duration: 25 minutes (intervals of 20 seconds:40 seconds)	≥70% peak power Duration: 25 minutes	5 x per week for 3 weeks
	Varga [300] n = 71 2007	Cycling in people with COPD	50% peak power interspersed with 10% peak power Duration: 45 minutes (intervals of 20 seconds:40 seconds)	≥70% peak power Duration: 45 minutes	3 x per week for 8 weeks
	Vogiatzis [26] n = 36 2002	Cycling in people with COPD	100% peak power and 45% peak power (intervals increased progressively to 140% peak power) Duration: 40 minutes (intervals of 30 seconds)	50% peak power, increasing to 70% by the end of the program Duration: 40 minutes	2 x per week for 12 weeks
	Vogiatzis [301] n = 19 2005	Cycling in people with COPD	100% peak power and 45% peak power, (intervals increased progressively to 140% peak power)	60% peak power, increasing to 70% by the end of the program Duration: 45 minutes	3 x per week for 10 weeks

			Duration: 45 minutes (intervals of 30 seconds)		
Additional studies	*Brønstad [294] n = 20 2013	Uphill treadmill walking in people with COPD	~ 90% maximal heart rate ('work') Duration: 38 minutes (intervals of 4 minutes: 4 minutes)	70% maximal heart rate Duration: 47 minutes	3 x per week for 10 weeks
	Rodriguez [293] n = 29 2016	Cycling in people with COPD	70 to 100% W_{peak} (progressively increased over the program), interspersed with 40 to 50% W_{peak} Duration: 40 minutes (intervals of 2 minutes: 3 minutes)	60% W_{peak} Duration: 40 minutes	3 x per week for 8 weeks

Abbreviations: 6MWT: 6-minute walk test, COPD: chronic obstructive pulmonary disease, W_{peak}: peak work rate. '*' identifies studies whereby the total work undertaken was unmatched between exercise training programs. The studies by Puhan et al. [296] and Varga et al. [300] report prescribing an intensity equivalent to 50% peak power of a steep-ramp test. This protocol is known to produce much higher maximal work rates than the traditional incremental ramp-based protocols. In both studies, the authors clarify that work rates equivalent to 50% of the maximum achieved on this test is the equivalent to approximately 90% of maximal work rate achieved during traditional protocols. Rodriguez et al. [293] reported that during the first 2 weeks of the program, cycling at high work rate was set to a minimum of 70% W_{peak} and was thereafter increased at 5% every week so that by week 3, training was being undertaken at a sufficiently high intensity to be classified as 'HIIT'.

Study or Subgroup	Interval Mean	SD	Total	Continuous Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Arnadottir 2007 (1)	11	20	28	11	22	32	17.7%	0.00 [-10.63, 10.63]
Coppoolse 1999 (2)	13	17	10	7	18	11	8.9%	6.00 [-8.97, 20.97]
Mador 2009 (3)	10	21	21	12	22	20	11.5%	-2.00 [-15.18, 11.18]
Nasis 2009 (4)	14	18	21	10	18	21	16.9%	4.00 [-6.89, 14.89]
Puhan 2006 (5)	9	27	44	9	19	46	21.3%	0.00 [-9.68, 9.68]
Rodriguez 2016 (6)	10	22	14	16	23	15	7.5%	-6.00 [-22.38, 10.38]
Varga 2007 (7)	14	37	22	12	37	17	3.7%	2.00 [-21.42, 25.42]
Vogiatzis 2002 (8)	14	25	18	13	21	18	8.8%	1.00 [-14.08, 16.08]
Vogiatzis 2005 (9)	10	28	10	9	24	9	3.7%	1.00 [-22.39, 24.39]
Total (95% CI)			**188**			**189**	**100.0%**	**0.73 [-3.74, 5.21]**

Heterogeneity: $Chi^2 = 1.69$, df = 8 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 0.32 (P = 0.75)

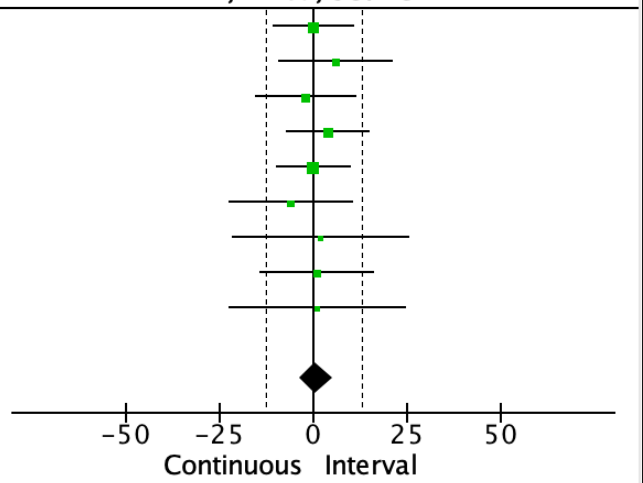


Figure 2.3 Comparison of effect of interval versus continuous exercise training on peak work rate (measured in Watts)

Footnotes:
(1) Within-group difference (W) and baseline SD
(2) Within-group difference (W) and baseline SD – paper reported within-group difference as a % of baseline. Value in Watts was calculated by the candidate.
(3) Within-group difference (W) and baseline SD
(4) Within-group difference (W) and baseline SD – paper reported SEM rather than SD. SD was calculated by the candidate.
(5) Within-group difference (W) and baseline SD
(6) Within-group difference (W) and baseline SD – paper reported within-group difference as a % of baseline. Value in Watts was calculated by the candidate.
(7) Within-group difference (W) and baseline SD – paper reported within-group difference as a % of baseline. Value in Watts was calculated by the candidate.
(8) Within-group difference (W) and baseline SD – paper reported SEM rather than SD. SD was calculated by the review authors. Paper reported within-group difference as a % of baseline. Value in Watts was calculated by the candidate.
(9) Within-group difference (W) and SD – paper reported SEM rather than SD. SD was calculated by the candidate.

Note: Dashed line indicates the suggested minimal clinically important difference for Watts (~10 W). Abbreviations: CI: confidence interval, SD: standard deviation, SEM: standard error of the mean, W: Watts.

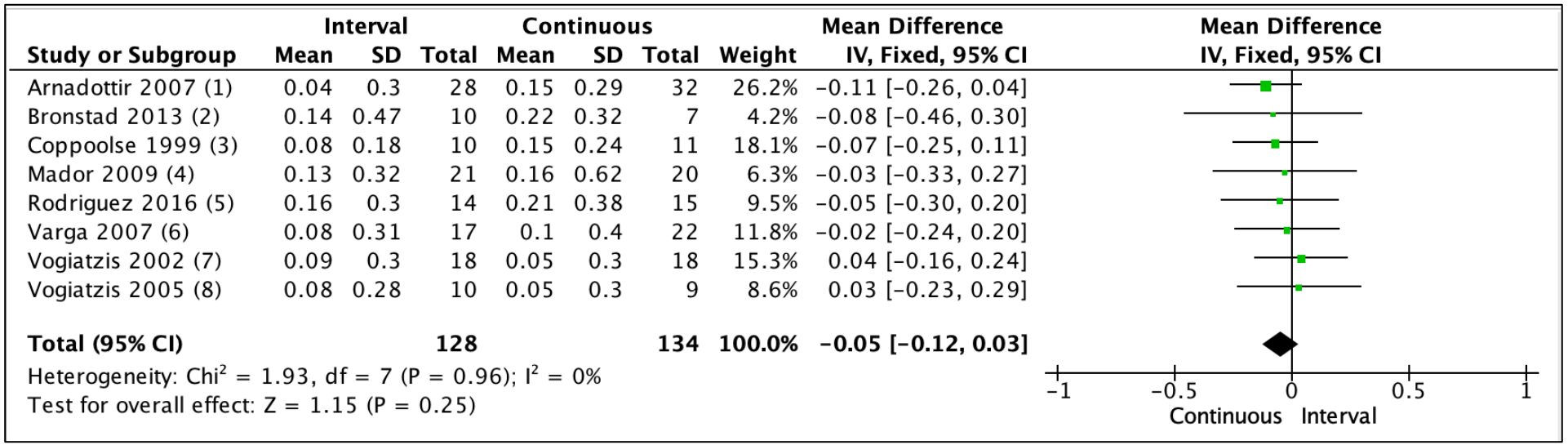


Figure 2.4 Comparison of effect of interval versus continuous exercise training on peak oxygen uptake (measured in L·min^{-1})

Footnotes:
(1) Within-group difference (L·min^{-1}) and baseline SD
(2) Within-group difference (L·min^{-1}) and baseline SD – paper reported within-group difference as a % of baseline. Value in L·min^{-1} was calculated by the candidate.
(3) Within-group difference (L·min^{-1}) and baseline SD
(4) Within-group difference (L·min^{-1}) and baseline SD – paper reported SEM rather than SD. SD was calculated by the candidate.
(5) Within-group difference (L·min^{-1}) and baseline SD
(6) Within-group difference (L·min^{-1}) and baseline SD – paper reported within-group difference as a % of baseline. Value in L·min^{-1} was calculated by the candidate.
(7) Within-group difference (L·min^{-1}) and baseline SD – paper reported within-group difference as a % of baseline. Value in L·min^{-1} was calculated by the candidate.
(8) Within-group difference (L·min^{-1}) and baseline SD – paper reported SEM rather than SD. SD was calculated by the review authors. Paper reported within-group difference as a % of baseline. Value in L·min^{-1} was calculated by the candidate.
(9) Within-group difference (L·min^{-1}) and SD – paper reported SEM rather than SD. SD was calculated by the candidate.

Note: Minimal clinically important difference not included as the value is unknown for VO_{2peak} in chronic obstructive pulmonary disease.

Abbreviations: CI: confidence interval, SD: standard deviation, SEM: standard error of the mean, VO_{2peak}: peak rate of oxygen uptake.

2.5.3 Cystic fibrosis

Earlier work suggests that HIIT is feasible in people with CF [34, 302, 303], including those who are characterised by severe expiratory airflow obstruction [34]. In a study by Armeniakou et al. [169], 14 adults with CF (aged 22 ± 4 years, 5 males) and 10 healthy adults serving as a control group (aged 29 ± 4 years, 5 males) underwent maximal and submaximal, endurance cycle ergometry exercise tests on the same assessment day, separated by 1 hour. The maximal test was a 'traditional' symptom-limited CPET test on a cycle ergometer. The second test was completed at 80% of the work rate matching the anaerobic threshold derived during the CPET. Adults with CF were found to have significantly slower phase two oxygen uptake kinetics (tau) compared to healthy adults [169]. The tau has been used as an index of exercise intolerance in other chronic cardiorespiratory conditions, such as COPD and heart failure [304-306]. Similar to data collected in COPD, this study supports the notion that rapid fluctuations in work and rest intervals are likely to be beneficial in people with CF, as the gas exchange kinetics are too slow to 'catch' the work intervals.

To date, there are no studies that have compared the effects of HIIT to no exercise in this population. Only two studies have compared HIIT with continuous exercise (Table 2.3). In one study (n = 23), participants (aged 26 ± 10 years, FEV_1 32 ± 4% predicted) completed, where possible, a continuous training program on a treadmill (45 minutes of exercise at 60 to 70% VO_{2peak}) and were only allocated to the HIIT group (aged 26 ± 8 years, FEV_1 26 ± 8% predicted) if they were unable to tolerate continuous training. The HIIT program comprised 30 seconds of walking at the individual's comfortable continuous walking speed (between 3 and 4 km/h) at 50% of the grade achieved during a steep-ramp test on a treadmill (modified Balke-protocol) interspersed with 60 seconds of rest (walking at 0% treadmill inclination). This work to rest ratio was repeated 10 times. On completion of the training program, both groups improved their VO_{2peak} (21 ± 4 to 23 ± 7 $mL \cdot kg^{-1} \cdot min^{-1}$ in the HIIT group, and 21 ± 7 to 25 ± 7 $mL \cdot kg^{-1} \cdot min^{-1}$ in the continuous exercise training group; difference in VO_{2peak} between groups was −1 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI −5 to 3]). Participants in the HIIT group reported the program to be 'motivating and less strenuous' than their previous experience with moderate intensity continuous exercise. These results must be interpreted with caution because, in this study, group allocation was not decided through a process of randomisation [34]. In addition, while the authors refer to the intervention as HIIT, the equivalent VO_{2peak} and W_{peak} achieved during the work intervals are not described. However, in comparison to previously mentioned studies in COPD [296, 300], 50% of the

intensity achieved on a steep-ramp test is equivalent to approximately 90% of W_{peak} achieved during traditional exercise protocols.

To our knowledge, only one RCT (available as a conference abstract only) has compared HIIT to moderate intensity continuous exercise in adults with CF (n = 24, age and FEV_1 not reported) [60]. In this study, participants were randomised to 12 weeks of HIIT (n = 12) or continuous exercise (n = 12). The training programs were matched for total volume of work. The HIIT and continuous exercise group improved their W_{peak} by 12% (89 ± 56 W to 108 ± 60 W) and 8% (93 ± 49 W to 109 ± 59 W), respectively. However, although the magnitude of between-group change was similar, the 95% confidence interval was wide and offered little precision (MD 1 W, 95% CI −51 to 49). Similar results were reported for 6MWD, with increases of 45 m (538 ± 70 m to 583 ± 83 m) and 48 m (516 ± 57 m and 564 ± 55 m) in the HIIT and continuous groups, respectively (MD 19 m, 95% CI −41 to 79) [60]. Despite being matched for the total volume of work undertaken during the training program, when compared with the continuous group, the HIIT group reported lower peak dyspnoea scores (4 ± 1 versus 6 ± 1 [MD 2, 95% CI −3 to −1]) and higher nadir SpO_2 (94 ± 1% versus 91 ± 1% [MD 3%, 95% CI 2 to 4]). This suggests that HIIT may be a more tolerable mode of exercise training in adults with CF.

Table 2.3 Description of studies comparing high intensity interval training with continuous exercise training in adults with cystic fibrosis

Study	Population	Interval exercise	Continuous exercise	Frequency and duration
Gruber [34] 2014 n = 23	Adults (medically stable inpatients)	1:2 work recovery ratio (30 seconds : 60 seconds, 20 seconds : 60 seconds if more deconditioned) on a treadmill. Speed 3 to 4 km/h (work) and 50% incline, 0% incline (active recovery) Duration: 16 minutes (10 interval bouts)	Various sport activities depending on fitness level (i.e. walking, ball games, stretching, balance training and resistance training). HR corresponding 80–90% equivalent to 60 to 75% VO_{2peak} (unmatched workload between groups) Duration: 45 minutes	5 times per week for 6 weeks
Kaltsakas [60] 2017 n = 24	Adults	30 seconds 100% W_{peak} interspersed with 40% W_{peak} for 30 seconds Duration: 30 minutes	70% W_{peak} (matched workload between groups) Duration: 30 minutes	12 weeks (frequency per week not provided)

Abbreviations: HR: heart rate, VO_{2peak}: peak rate of oxygen uptake, W_{peak}: peak work rate.

2.5.4 Non–cystic fibrosis bronchiectasis

There appears to be no published studies that have investigated the effects of HIIT in people with non-CF bronchiectasis.

2.5.5 Asthma

Although one of the first uncontrolled studies investigating high intensity exercise in people with asthma was undertaken in 1996 [307], to date, only one RCT has evaluated the effect of HIIT compared to usual care (i.e. no exercise) on exercise capacity in this population [308]. In this RCT, untrained people with asthma were allocated to undertake an 8-week intervention period consisting of thrice-weekly HIIT (n = 20, aged 39 ± 13 years, FEV_1/FVC 0.91 ± 0.01) on a cycle ergometer, compared with a usual care group (i.e. no formal exercise training) (n = 34, aged 38 ± 13 years, FEV_1/FVC 0.85 ± 0.01). For participants allocated to receive the HIIT, each session comprised a 10-minute warm-up at a low intensity, followed by consecutive 1-minute exercise bouts for a 5-minute period. The intensity achieved during each minute of exercise was dynamic, with a relative rest and high intensity exercise integrated into each minute bout. That is, the first 30 seconds was undertaken at < 30% of the HR_{max} (relative rest), the second 20 seconds was undertaken at < 60% of the HR_{max}, and the final 10 seconds was undertaken at > 90% of the HR_{max} (high intensity). The 5-minute sets were repeated twice in the first 2 weeks, and progressively increased up to four sets throughout the intervention period. Each training session concluded with a 10-minute cool-down. This type of HIIT intervention was reported to be well tolerated and elicited an increase in VO_{2peak} that was over and above any change in the usual care group (between-group difference in VO_{2peak} 3 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$, $p < 0.0001$) [308, 309]. However, the authors speculate that achieving a heart rate of > 90% of the HR_{max} within a 10-second period may be difficult to replicate in clinical practice. In addition to the effects of HIIT compared to usual care, one RCT (results reported in a conference abstract; n = 16 in the HIIT group, no data on age or respiratory function) demonstrated that HIIT offered comparable benefits to moderate intensity continuous exercise, albeit with lower overall symptoms of dyspnoea [310]. In this study, the HIIT group undertook 30-second work bouts at 80 to 140% of the W_{peak}. This training regimen was compared with continuous exercise at 70 to 85% of the HR_{max}. Similar improvements in VO_{2peak} were demonstrated following both modes of exercise (unable to calculate 95% CI from data provided). In addition, dyspnoea was lower during HIIT compared to continuous exercise ($p < 0.05$, unable to calculate 95% CI from data provided).

Nevertheless, one contentious issue regarding HIIT for people with asthma is whether or not it is more or less likely to cause exercise-induced bronchoconstriction. Specifically, some, but not all, studies have reported more modest decreases in FEV_1 in response to HIIT (90% W_{peak} for 1 minute followed by 10% of W_{peak} for 1 minute, repeated 10 times; FEV_1 −7% ± 8%) when compared with moderate intensity continuous training programs (completed at 65% W_{peak}; FEV_1 −15% ± 12%) [36, 311]. Similarly, the effects of HIIT compared with continuous training approaches on dyspnoea and rating of perceived exertion experienced during training are also disparate [312, 313]. Studies which included a warm-up period, rather than commencing with work intervals by cycling 'as fast as possible' without any resistance on the pedals, appeared to induce less bronchoconstriction [311]. When applying HIIT, clinicians should consider offering a warm-up period and monitor FEV_1 and symptoms for evidence of exercise-induced bronchoconstriction.

2.5.6 Interstitial lung diseases

Despite the recognised benefit of exercise training for people with ILDs [24, 314-317], there are currently no published studies evaluating the effects of HIIT, compared to usual care or continuous exercise, in people with these conditions. A group of researchers from Melbourne, Australia, are currently undertaking an RCT in this field (ACTRN12619000019101). Nevertheless, a recent conference abstract reported data collected in a small group of people with ILD (n = 6, age and FVC not reported) [318] showing comparable levels of dyspnoea and leg muscle fatigue during HIIT (100% W_{peak} for 30 seconds interspersed with 30 seconds of unloaded cycling; modified Borg 4 ± 2 and Borg 13 ± 4, respectively) and moderate intensity continuous exercise (60% W_{peak}; modified Borg 3 ± 1 and Borg 13 ± 5, respectively). Similarly, HIIT was undertaken with comparable exercise heart rates and nadir SpO_2, despite a higher overall training workload for the HIIT compared to moderate intensity continuous exercise [318].

2.5.7 Lung cancer

A couple of studies have reported the feasibility and safety of incorporating a component of HIIT in exercise training interventions for people with NSCLC [319, 320]. One RCT compared the effects of short-term HIIT (median [IQR] number of sessions = 8 [7 to 10] in 26 [21 to 33] days) with usual care in people with NSCLC, prior to lung resection surgery [321]. Participants allocated to receive HIIT (n = 74, aged 64 ± 13 years, FEV_1 86 ± 22% predicted) were asked to attend three exercise sessions per week with a therapist present (variable length of program according to date of surgery). The HIIT comprised a 5-minute warm-up (50% W_{peak}), followed by a 10-minute bout of 15-second sprints (80 to

100% W_{peak}) interspersed with 15 seconds of low-intensity exercise (30% W_{peak}). This HIIT set was separated by a 4-minute rest, and then repeated (i.e. two 10-minute sets were completed per training session). Compared with a control group that received no formal exercise training (n = 77, aged 64 ± 10 years, FEV_1 88 ± 19% predicted), the HIIT group demonstrated greater improvements in VO_{2peak} on completion of the training program (MD 4 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 2 to 6) [321]. Studies comparing the effects of HIIT with moderate intensity continuous exercise in people with this condition are lacking.

2.5.8 Conclusions and future directions for high intensity interval training in chronic respiratory conditions

In people with COPD, HIIT produces gains in exercise capacity when compared with no training. The magnitude of these gains appears to be similar to those achieved with continuous exercise. In people with CF, non-CF bronchiectasis and ILDs, there are currently no RCTs evaluating the effects of HIIT compared to usual care or to moderate intensity continuous exercise. Nevertheless, in people with CF and ILDs, there are data to show that HIIT is well tolerated. High intensity interval training in people with asthma is somewhat contentious, owing to the variable effects on bronchoconstriction and symptoms during exercise. Data from one RCT [321] supports the use of pre-operative HIIT (compared to usual care) in people with NSCLC to increase exercise capacity. However, the effects of HIIT compared with moderate intensity continuous exercise in people with NSCLC are unknown.

Some studies (particularly those with shorter work to rest intervals) have shown superior improvement in exercise capacity (workload) with comparable improvements in cardiorespiratory fitness (VO_{2peak}), favouring HIIT. Additionally, 70% of studies included within this narrative review prescribed interventions whereby the total volume of work was matched between the HIIT and continuous exercise interventions. That is, the overall training load borne was equivalent between the HIIT and continuous exercise, which is likely to explain why similar effects were demonstrated between the two modes of exercise training in most studies. As such, future studies, particularly in people with COPD, are needed to determine whether HIIT, during which a smaller total training load is prescribed, can produce comparable or superior benefits in exercise capacity and cardiorespiratory fitness to continuous exercise. This review emphasises the need for large RCTs to investigate the effects of HIIT compared to usual care and HIIT compared to moderate intensity continuous exercise in most chronic respiratory populations.

2.6 Summary

Cystic fibrosis is a genetic, multi-system disease, which has a profound effect on the respiratory system and results in premature death or the need for lung transplantation [45]. Increasing life expectancy of people with CF has resulted in an ever-increasing treatment burden across the lifespan [47]. Reduced exercise capacity is a common characteristic of CF [48]. Exercise training is safe, and demonstrated to be an effective method to optimise exercise capacity in this population [3]. However, a significant proportion of people with CF do not adhere to the current exercise treatment guidelines of 30 to 60 minutes of aerobic exercise on most days [4] due to time constraints [54]. High intensity interval training is beneficial for people with a chronic cardiorespiratory condition, such as COPD [35]. Data related to the effectiveness of HIIT on exercise capacity in people with CF are sparse [34, 60] and further RCTs are warranted.

CHAPTER 3

A SURVEY OF EXERCISE TESTING AND TRAINING IN CYSTIC FIBROSIS CENTRES ACROSS AUSTRALIA AND NEW ZEALAND

Overview

This chapter presents the background, methodology, results and discussion of a survey performed as part of this program of research. Prior to this survey being undertaken, there were no published data pertaining to the extent and scope of, and importance placed on, exercise testing and exercise training within Australian and New Zealand cystic fibrosis (CF) centres. This survey was published in the *Internal Medicine Journal* in August 2019 [162]. A full version of the survey can be found in Appendix 2.

3.1 Introduction

Exercise testing and exercise training are common components of the clinical care of people with CF [37, 161]. Regarding testing, international recommendations support the completion of annual laboratory-based exercise testing (i.e. a cardiopulmonary exercise test [CPET]) to identify exercise intolerance and guide exercise prescription, and for prognostication [38, 39]. Work done over 10 years ago in the United Kingdom and Germany reported that annual

CPET data were collected on less than 50% of people living with CF, with its uptake compromised by cost, and the need for specialised equipment and technical expertise to conduct these tests [40, 41]. Field-based exercise tests, such as the 6-minute walk test (6MWT) or incremental shuttle walk test (ISWT), are likely to have greater clinical utilisation [42].

Regarding participation in daily physical activity and/or exercise training, clinical CF guidelines currently recommend people to complete 30 to 60 minutes of moderate intensity aerobic exercise on most days [4]. This recommendation aligns with that made for the general adult population [12, 43, 44]. Current practices regarding advice to participate in regular physical activity or the provision of exercise training programs within Australian and New Zealand CF centres are unclear.

This study sought to answer the following research question: what is the extent and scope of, and importance placed on, exercise testing and exercise training in Australian and New Zealand CF centres? Specifically, we sought to explore differences in: (i) the utility of annual exercise testing; (ii) the nadir peripheral capillary oxygen saturation (i.e. cut-off value), below which testing and training would be terminated (or rests imposed); and (iii) the proportion of CF centres that provide an exercise training program.

3.2 Study design

3.2.1 Sample

Health professionals from CF centres within Australia and New Zealand with knowledge or direct involvement in exercise testing and training were eligible to respond to the survey. A list of CF centres was compiled using online resources from Cystic Fibrosis Australia and Cystic Fibrosis NZ websites.

3.2.2 Instrument

A survey was developed using the online platform *Qualtrics*. Three cardiorespiratory physiotherapists in Perth, Western Australia, who were not involved in the study, completed a pilot version. Survey questions were then modified to optimise readability and reduce ambiguity.

The final version of the survey comprised five sections and a maximum of 46 questions (summary provided in Table 3.1; for full questionnaire, see Appendix 2). At the end of each section, participants were asked to rate the importance placed on exercise testing and training practices within their CF centre [40, 41]. As the survey used an automatic skip function to avoid participants completing questions that were not applicable, the survey took between 5 and 20 minutes to complete.

Table 3.1 Questions used in the survey that pertained to exercise testing and exercise training

Exercise testing	Exercise training
Location of exercise testing	Health professionals involved
Equipment readily available for exercise test	Exercise training discussion time points
Type of exercise test completed (and protocol)	Type (if any) of outpatient exercise training program
Reason(s) for undertaking exercise test	Referral and triage process
Proportion of patients who completed exercise test in the preceding 12 months	Prescription and progression of exercise training program
The health professional responsible for undertaking the exercise test	Threshold used for nadir peripheral capillary oxygen saturation
Threshold used for nadir peripheral capillary oxygen saturation permitted	Supervision provided (if any)
Staff availability	Mode of exercise training
Limitations to exercise testing	Equipment used for monitoring
Importance placed on exercise testing	Importance placed on exercise training

3.2.3 Approach

Contact was made with each CF centre via email and/or telephone between November 2018 and March 2019. At initial contact, the details were requested of the health professional who most commonly managed exercise testing and/or training for people with CF at the centre. An email containing a link to the online survey was then distributed to this person.

The survey response rate was optimised using the approach proposed by Dillman and colleagues [322]. One month was allowed for completion of the online survey and if no response was received during this period, a reminder email was sent. This process was repeated for three consecutive months, and if no response was received after the third email reminder, a final attempt was made to contact the designated respondent by phone. Following this attempt, no further attempts at contact were made [322, 323].

3.2.4 Analysis

Survey responses were collated automatically via *Qualtrics* and then exported into a Microsoft Excel spreadsheet. Results are presented in absolute values (i.e. number of respondents) and/or as a percentage of respondents. Where relevant, between-group differences in proportion of respondents or responses were analysed using two proportion z-tests (STATA, version 15, Texas, USA).

3.3 Results

A total of 45 sites were identified. Of the 24 and 21 sites identified in Australia and New Zealand, respectively, five were excluded as they did not have a current designated CF service or offered sporadic outreach or 'visiting' clinics. Initial contact was made with respondents from 40 sites (22 sites in Australia and 18 in New Zealand). Following the initial attempt, 14 survey responses were received, and one centre declined to undertake the survey. A second contact attempt yielded a further 10 responses. Fifteen centres were contacted on a third occasion by email and then attempted phone calls, with a further eight centres completing the survey. A total of 32 surveys were completed (response rate: 80%). The response rate from Australian and New Zealand centres was 19 of 22 (86%) and 13 of 18 (72%), respectively (difference: 14%; 95% confidence interval [CI] −11 to 39).

3.3.1 Characteristics of respondents and centres

Respondents described a median of 10 years (range: 2 to 35 years) of clinical experience in the area of CF and were physiotherapists (n = 28/32; 88%), nurses (n = 2/32; 6%), a physician (n = 1/32; 3%) and a respiratory physiologist (n = 1/32; 3%). Fifteen respondents (47%) worked in adult centres, 11 (34%) worked in paediatric centres, and six (19%) were from centres that managed paediatric and adult patients. The median number of people with CF known to each centre was 94 (range: 3 to 430 people), with the clinical care of 3,937 patients represented overall (Australia: n = 3,530; New Zealand: n = 407). A median of 195 (range: 6 to 430) people were known to each centre in Australia, whereas a median of 22 (range: 3 to 94) people were known to each centre in New Zealand.

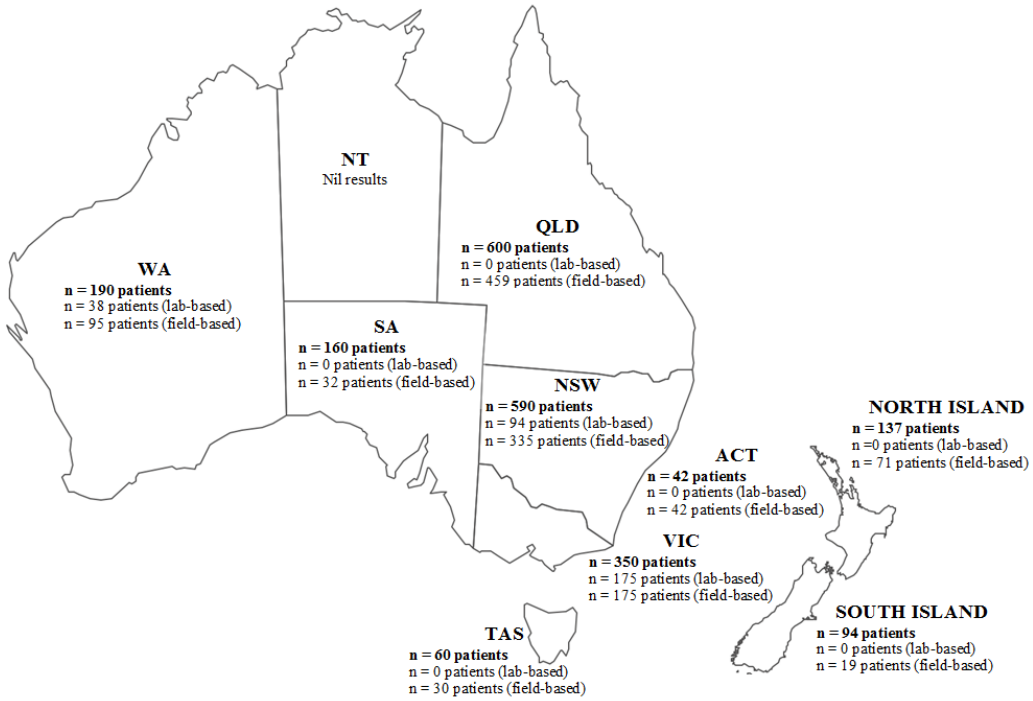


Figure 3.1 Representation of adults living with CF across Australia and New Zealand who received laboratory-based and field-based exercise tests in the preceding 12 months

Estimated number of patients represented in survey: 3,937. Of these, an estimated 2,223 patients were adults. Survey respondents were asked to indicate the % of patients who received laboratory-based and field-based exercise tests in the preceding 12 months (none; the minority [0 to < 20%]; under half [20 to <50%]; about half [~50%]; over half [50 to < 70%]; almost all; unsure). The numbers assigned (in this figure) to laboratory- and field-based tests represent the upper limit of the indicated range provided by respondents.

Abbreviations: ACT: Australian Capital Territory, NSW: New South Wales, NT: Northern Territory, QLD: Queensland, SA: South Australia, TAS: Tasmania, VIC: Victoria, WA: Western Australia.

3.3.2 Exercise testing

3.3.2.1 Uptake

Of the 32 respondents, 11 (34%) reported that their centre had completed laboratory-based exercise testing for patients with CF within the preceding 12 months. Almost all respondents reported that their CF centre had completed field-based exercise testing within the preceding 12 months (n = 28/32; 88%). The difference in the number of centres completing laboratory-based versus field-based exercise testing within the preceding 12 months was 54% (95% CI 31 to 70). Regarding laboratory-based exercise testing, most centres that reported completing this test in the preceding 12 months (n = 7/11; 64%) had performed these tests on ≤20% of patients. Regarding field-based exercise tests, respondents that reported completing this test in the preceding 12 months had performed these tests on the minority (n = 4/28; 14%), under half (n = 9/28; 32%), about half (n = 3/28; 11%), more than half (n = 9/28; 32%) or almost all (n = 2/28; 7%) of their patients. A respondent from one centre reported being 'unsure'. As infants and children managed within paediatric centres would not be capable of undertaking exercise testing, data presented in Figure 3.1 pertaining to the (estimated) number of people with CF who undertook exercise testing (according to location) have been calculated using adults centres only.

3.3.2.2 Reasons for and limitations to exercise testing

Reasons for completing laboratory-based and field-based exercise testing are summarised in Table 3.2. The most common reasons for undertaking a laboratory-based exercise test were 'patients reporting reduced exercise tolerance' (n = 8/11 centres; 73%) and 'for research' (n = 7/11 centres; 64%). Limited availability of staff was the most common barrier to undertaking laboratory-based exercise tests (n = 8/24 reports; 33%).

The most common reason for undertaking a field-based exercise tests was as part of the annual review assessments (n = 21/28 centres; 75%). The most common barrier for undertaking these tests was the availability of staff (n = 17/28 centres; 61%) (Table 3.3).

Table 3.2 Reasons for exercise testing being undertaken

Reason	Laboratory-based tests; 29 responses from 11 centres	Field-based tests; 99 responses from 28 centres
Annual review	1	21
Patient reports reduced exercise tolerance	8	18
Pre-transplant assessment	1	17
To investigate the effect of a therapeutic intervention	5	12
Exercise prescription	4	13
Research	7	11
Other	3	7

Respondents at each CF centre were permitted to choose more than one response. Results indicate the number of times the response was selected.

Table 3.3 Barriers to completing exercise testing

Limitations	Laboratory-based tests; 24 responses from 11 centres	Field-based tests; 53 responses from 28 centres
Staffing availability	8	17
Staff training	2	1
Equipment limitations	1	2
Equipment availability	4	1
Not viewed as important	1	3
Infection control precautions	1	2
Patient declines to complete	2	15
Other*	5	12

Respondents at each CF centre were permitted to choose more than one response. Results indicate the number of times the response was selected.
* CF-specific exercise laboratory/space, need for more research output, need for formal exercise testing protocols, support from medical staff.

3.3.2.3 Protocol and equipment

Of the 11 centres that had completed laboratory-based exercise tests, four (36%), two (18%) and four (36%) reported using a cycle ergometer, a treadmill, or either a cycle and/or treadmill, respectively. One centre used a cycle ergometer and/or a laboratory-based step test (9%). For cycle ergometery and treadmill tests, work rate was increased using an incremental ramp-based protocol in 10 of the 11 centres (91%). Equipment most commonly used for monitoring were pulse oximetry (n = 10/11, 91%), an electrocardiogram (ECG) (n = 10/11; 91%) and a metabolic cart for expired gas analysis (n = 8/11; 73%).

Of the 28 centres that had completed field-based exercise tests, the 6MWT and ISWT were undertaken most commonly (25/28 [90%] and 23/28 [82%] centres, respectively). Step tests and endurance shuttle walk tests were undertaken in 10 (36%) and four centres (14%), respectively (Table 3.4). Monitoring equipment included pulse oximetry (n = 27/28; 96%) and an ECG (n = 2/28; 7%).

Table 3.4 Type of exercise test used in cystic fibrosis centres in Australia and New Zealand

Type of test	Name of test	Paediatric	Adult	Mixed	Overall
Laboratory-based (n = 11 centres)	Treadmill test	4	0	1	**5**
	Cycle ergometry test	3	4	1	**8**
	Step test	0	1	0	**1**
Field-based (n = 28 centres)	6MWT	6	15	4	**25**
	ISWT	8	11	4	**23**
	ESWT	2	2	0	**4**
	Step test	4	2	4	**10**

Respondents at each CF centre were permitted to choose more than one response. Results indicate the number of times the response was selected.
Abbreviations: 6MWT: 6-minute walk test, ESWT: endurance shuttle walk test, ISWT: incremental shuttle walk test.

3.3.2.4 Location

Of the 11 centres that had completed laboratory-based exercise tests, five (45%) used a CF-specific laboratory with the rest using a non-CF-specific laboratory. Field-based exercise tests were most commonly performed in an outpatient department (i.e. physiotherapy) (n = 24/28; 86%), on the ward (n = 5/28; 18%), in the CF clinic (n = 9/28; 32%) or in a gymnasium (n = 8/28; 29%).

3.3.2.5 Personnel

Laboratory-based exercise tests were conducted by a respiratory scientist (n = 9/11; 82%) or a physiotherapist (n = 2/11; 18%). In five centres (46%), a doctor was required to be present during all laboratory-based exercise tests. Field-based exercise tests were facilitated by a physiotherapist (n = 28/28; 100%), with five centres (18%) also using respiratory scientists to complete these tests.

3.3.2.6 Threshold for arterial oxygen desaturation during exercise testing

Five (45%) of 11 centres used a nadir peripheral capillary oxygen saturation measured via pulse oximetry (SpO_2) below which laboratory-based exercise tests would be terminated. This cut-off value was 85% in four (36%) centres and 80% in one (9%) centre. The other six centres reported either being unsure (n = 3/11; 27%) or having no set cut-off value in place (n = 3/11; 27%). Regarding field-based exercise testing, five (18%) centres used a nadir SpO_2 below which the test would be terminated or a rest would be imposed. This SpO_2 cut-off value was 85% in five centres (18%) and 80% in another five centres (18%). The other 18 centres (64%) reported either being unsure (n = 3/28; 11%) or having no set cut-off value (n = 15/28; 54%). The use of a cut-off value for SpO_2 tended to be more common for laboratory-based tests than field-based tests (difference: 27%; 95% CI −3% to 55%).

3.3.2.7 Importance placed on exercise testing

Comments regarding exercise testing are provided in Table 3.5 (Comments 1 to 5). The importance placed on laboratory-based and field-based exercise tests is shown in Table 3.6.

3.3.2.8 Strength testing

Muscle strength testing was undertaken in six (19%) CF centres across Australia and New Zealand. When strength was assessed, it was most often done using a hand-held dynamometer (n = 4/6; 67%).

Table 3.5 Written comments provided by respondents

	Additional comments offered by respondents
Exercise testing	1. "Medical team hoping to implement CPET testing on a yearly basis – but limited by staffing currently – business case currently in place." 2. "Our difficulty, like many centres, is trying to perform testing on most appropriate patients to guide interventions. The volume is great and the availability of space to get through the volume is also problematic." 3. "Sometimes I will bring a patient in for exercise testing if it is required but this is difficult to arrange with a busy inpatient caseload." 4. "Most commonly [CPETs] are used to investigate further if there have been significant changes in field testing (e.g. ISWT or six minute walk) or if there is a suspicion of abnormality. Some patients have had CPET as part of clinical trials."
Both	5. "For patients with higher exercise tolerance, [I] aim to complete incremental shuttle in clinic, but it is a shared space so patients have to wear a mask limiting the results. Supervised exercise [training] is offered to patients not completing any exercise, post exacerbation or with deterioration in function. It is provided by the ward physio in the inpatient gym so space and time are issues."
Exercise training	6. "Often community-based activities are encouraged. Rarely use outpatient classes such as pulmonary rehab due to risk to CF patient." 7. "Limitations on numbers of people able to be seen due to infection control issues in the gym." 8. "There is a considerable amount of support from local CF association to overcome any financial barriers to gym memberships or equipment in the home. Due to the hospital layout, space, lack of equipment and infection control concerns, exercise has not been promoted or supported well in the hospital setting inpatients or outpatients and is an area that needs to improve." 9. "Training is very limited at our centre, we have no outpatient service for CF, so we are unable to complete gym strength session unless it is done during inpatient admissions." 10. "Supervised exercise is provided by the ward physio in the inpatient gym, so space and time are issues." 11. "It [exercise training] is highly variable, largely based on patient preference. We do refer to local hospitals for our outer metro or country patients. Our health department policies on telehealth mean the value of this is limited – they are better off just being referred to a local clinician – this will hopefully change in the near future so telehealth in the patients' home will be available." 12. "Patients are seen for exercise more specifically if they are approaching transplant or on the list. Most children are doing some form of activity but this is mainly a sport through school. Exercise is always discussed and recommended...limited funding in this area as my role is only 0.1FTE." 13. "We have limited capability to supervise exercise programs."

Abbreviations: CF: cystic fibrosis, CPET: Cardiopulmonary exercise test, FTE: full-time equivalent, ISWT: incremental shuttle walk test.

3.3.3 Exercise training

3.3.3.1 Healthcare professionals who discussed physical activity/exercise

Advice regarding physical activity and/or exercise was provided at all centres (n = 32/32). This advice was most often provided by physiotherapists (n = 29/32; 91%), but was also being offered by physicians and nurses in 19 (59%) and 13 (41%) centres, respectively. Physical activity and/or exercise was discussed at every clinic visit in 27 (84%) centres and during the annual review in 10 centres (31%). A smaller proportion of respondents indicated that discussion occurred only if a patient asked (n = 3/32; 9%) or for 'other reasons' (n = 5/32; 16%) such as during admissions or 'extra' (non-routine) outpatient appointments.

3.3.3.2 Provision and referral process

A total of 24 of 32 (75%) respondents indicated that their centre provided access to an outpatient exercise program and, of these, 22 (92%) described offering an individually tailored program. There were five (21%) reports of centres providing a standardised outpatient exercise program. Referrers to these programs comprised the physiotherapist who worked with the CF team (n = 20/24; 83%), the person with CF (n = 11/24; 36%), the medical team (n = 14/24; 58%) and/or another health professional (n = 9/24; 38%). Five respondents (21%) indicated that all people with CF were referred for an exercise program (i.e. a 'blanket' referral process), and two (8%) respondents were unsure of who referred to the program. Referrals were most frequently triaged according to disease severity (n = 14/24; 58%) and if patients were immediately post-discharge (n = 11/24; 46%). Four respondents reported there being no specific triage system (16%) and one respondent was unsure (4%).

3.3.3.3 Prescription and progression

Factors used to prescribe the intensity of exercise training included the results of laboratory-based exercise tests (n = 5/24; 21%), field-based exercise tests (n = 16/24; 67%), the predicted maximal heart rate (n = 18/24; 75%), SpO_2 readings (n = 21/24; 88%) and/or symptom scores (n = 22/24; 92%). One (4%) respondent reported being unsure. The progression of exercise intensity was titrated using symptom scores (n = 19/24; 79%), SpO_2 (n = 17/24; 71%) and/or heart rate responses (n = 15/24; 63%). There were eight (33%) and one (4%) report of field-based exercise tests and laboratory-based exercise tests, respectively, being used to progress exercise intensity. The majority of respondents (n = 16/24; 67%) reported that either moderate intensity continuous exercise or interval training was prescribed based on symptoms and patient preference.

3.3.3.4 Threshold for arterial oxygen desaturation during exercise training

Of the 24 centres that offered a supervised exercise training program, four (17%) reported using a cut-off value for SpO_2 of 85%, below which the training would be interrupted. Seventeen centres (71%) reported having no specific cut-off value in place and three (12%) reported being unsure of a SpO_2 cut-off value.

3.3.3.5 Therapist presence

Exercise training was undertaken either with a therapist entirely present (n = 16/24; 67%), partially present (n = 5/24; 21%) or via telehealth (n = 1/24; 4%). Two (8%) respondents were unsure of the level of supervision provided.

3.3.3.6 Importance and limitations

The importance placed on exercise training is shown in Table 3.6. A total of 18 respondents provided information regarding the limitation(s) to undertaking an exercise training program. The reasons provided included limitations in staff availability (n = 6/18; 33%), insufficient staff training (n = 1/18; 6%), equipment limitations/availability (n = 3/18; 17%), infection control precautions (n = 5/18; 28%) and other reasons (n = 3/18; 17%). Additional comments regarding exercise training are available in Table 3.5 Comments 6 to 13).

Table 3.6 Importance placed on exercise testing and training

Importance					
Type	**Not at all**	**A little**	**Somewhat**	**A lot**	**Very much**
Laboratory-based testing (n = 11 centres)	0%	3/11; 27%	7/11; 64%	0%	1/11; 9%
Field-based testing (n = 28 centres)	0%	3/28; 11%	11/28; 39%	6/28; 21%	8/28; 29%
Exercise training (n = 31 centres)	0%	3/31; 10%	9/31; 29%	10/31; 32%	9/31; 29%

Percentages relate to the proportion of CF centres selecting each level of importance. One respondent did not provide a response for the importance placed on exercise training in their centre.

3.4 Discussion

This survey describes the current exercise testing and training practices in Australian and New Zealand CF centres. The main findings of this survey were: (i) the majority of CF centres do not undertake laboratory-based exercise tests and, if performed, these tests are generally undertaken on the minority of patients; (ii) almost all CF centres undertake field-based exercise testing on at least half of their patients annually; (iii) participation in physical activity/exercise is discussed by at least one health professional in the CF team at every clinic appointment and/or at annual review; (iv) most centres offer some form of exercise training program to patients, though uptake of these programs is considerably limited by space, staffing and infection control precautions; and (v) a large proportion of centres do not have a cut-off value for SpO_2 below which exercise testing and training would be interrupted or ceased.

The response rate of 80% for this survey was significantly higher than in two previous international surveys (52% and 58%) [40, 41]. Additionally, the estimated number of patients represented in the current survey is similar to the most recently published Australian and New Zealand CF data registry reports. These factors suggest that the survey results are unlikely to be influenced by responder bias and the data are representative of the current practices in Australia and New Zealand.

International groups support the completion of annual laboratory-based exercise tests in people with CF, particularly those who are classified as 'high risk' [38, 39]. The results of this survey highlight the infrequent use of this type of exercise test in Australian and New Zealand CF centres. This finding is consistent with similar international survey data completed up to 15 years ago and suggests little change in the uptake of these tests [40, 41]. Not surprisingly, field-based exercise tests are the most utilised type of exercise test in Australian and New Zealand CF centres.

Despite the limited data regarding cardiorespiratory responses to exercise obtained during a 6MWT compared to a CPET, the former test can still contribute important information. In adults with CF (n = 286, median age 28 years [23 to 33 years], median FEV_1 45% predicted [32 to 65% predicted]), low 6-minute walk distance and desaturation were associated with poorer survival or need for lung transplantation [173]. Based on these data, field-based exercise tests may be recommended in the first instance in centres that have limited ability to undertake laboratory-based exercise tests. Similar to recommendations in other clinical populations, perhaps an algorithm to guide patient selection for laboratory-based tests would be useful to guide decision making. For example, for adults undergoing lung resection for

lung cancer [324], a field-based exercise test is performed initially and if the performance is poor (e.g. < 400 m on the ISWT), then a laboratory-based test is recommended [324]. Further work is required to support this suggestion and to extrapolate these findings to other commonly used field-based exercise tests and to the paediatric population [161, 164].

For people with CF, discussion of the importance of regular participation in physical activity and/or exercise are initiated by at least one health professional at clinic appointments and/or annual review appointments in Australian and New Zealand CF centres. In centres that did offer a training program, exercise prescription and progression were largely individualised and the parameters used to guide initial prescription and progression of exercise intensity varied greatly. Future research is needed to determine the training parameters that optimise both health outcomes and long-term adherence.

There was considerable disparity in the approach to managing arterial oxygen desaturation during exercise testing and training. A large proportion of centres reported having no protocol in place regarding a cut-off value for SpO_2 below which exercise would be ceased or interrupted. Guidelines for people with chronic respiratory conditions recommend that field-based exercise tests should be ceased in the event of severe desaturation (≤80% SpO_2) [161, 164]. Although in people with CF, maintenance of peripheral capillary oxygen saturation during exercise training may result in acute gains in exercise performance [325], the role of supplemental oxygen as a training adjunct in those who desaturate on exertion is unknown. This is a contentious issue in other chronic respiratory populations, with a recent study demonstrating that the provision of supplemental oxygen during exercise training offered no additional benefit in those with COPD who desaturate on exertion [28].

Finally, apart from staffing, one of the main limitations to implementing an outpatient exercise training program was related to the risk of cross-infection between people with CF. Considering emerging methods of exercise testing and training supervision, such as telehealth [326-328], which was reported in one centre, is likely to be an important alternative to reduce the risk of cross-infection.

3.4.1 Limitations

On a few occasions, the survey was completed by a member of the team who may not have been directly involved in exercise testing and training practices. Additionally, some respondents may have been involved in exercise testing, but not exercise training and vice versa, which may reduce the accuracy of the results. To limit the impact of this, respondents were encouraged to discuss questions with their colleagues if they were unsure of an answer.

Respondents were permitted to provide multiple responses, or no response (if their centre did not undertake exercise testing and training), for questions related to reasons for, limitations to performing, and importance placed on exercise testing and training. As smaller centres that did not undertake exercise testing or training were not required to answer questions regarding limitations to performing exercise testing and training, the data on limitations are most likely to reflect those experienced by large centres.

3.5 Conclusions

This survey captures the current practices of exercise testing and training in CF centres across Australia and New Zealand. Few centres undertake laboratory-based exercise tests, with time and cost cited as the most common barriers. The impact of undertaking these tests annually on clinical decision making and health outcomes in people with CF remains unanswered and should be a focus of future research. Most centres reported undertaking annual field-based exercise tests on most of their patients. The threshold for arterial oxygen desaturation during exercise testing and training was variable. A high proportion of centres offered some form of outpatient exercise training program. However, the provision of outpatient programs was limited by staffing, space and infection control concerns. This survey highlights the variability surrounding exercise testing and training practices across Australia and New Zealand, and can be used as a benchmark of current practice.

CHAPTER 4

EFFECTS OF HIGH INTENSITY INTERVAL TRAINING ON EXERCISE CAPACITY IN PEOPLE WITH CYSTIC FIBROSIS: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

Overview

This chapter presents the methodology of the single-blinded randomised controlled trial (RCT) undertaken as part of this PhD program of research. The methodology is relevant to Chapter 5 (baseline results) and Chapter 6 (main results and discussion). Details are provided of the inclusion and exclusion criteria, recruitment strategies, and the randomisation and blinding process. The assessment protocol and measurements made before and after the intervention period are described. The experimental and control group regimens, as well as data management and statistical analyses used to assess the effects of low-volume high intensity interval training (HIIT) are also described. The chapter expands on the study protocol published in *BMC Sports Science, Medicine and Rehabilitation* in November 2018 [61]. A published version of this protocol is available at: https://dx.doi.org/10.1186%2Fs13102-018-0108-2.

4.1 Study design

This study was a prospective single-blinded RCT. A study design flow diagram is available in Figure 4.1. Data collection took place between October 2017 and October 2019. After providing written informed consent, participants completed their initial (i.e. baseline) assessment period. Following the baseline assessment period, participants were randomised to the experimental group or the control group, and completed an 8-week intervention period. On completion of the intervention period, those in the experimental group were invited to attend a 'debrief' audio-recorded interview and participants in both groups completed a follow-up assessment period.

During the intervention period, both groups received usual care (e.g. medication, airway clearance techniques, nutritional support and clinic attendance). Those allocated to the experimental group also participated in HIIT twice in the first 2 weeks, increasing to thrice-weekly from week 3 to week 8 of the program. Sessions were overseen by the same physiotherapist (PhD candidate). Those in the control group were contacted weekly by the PhD candidate and asked about their level of exercise participation, symptom changes (if any) and whether they had any contact with their cystic fibrosis (CF) team.

4.1.1 Ethics approval and trial registration

The study was approved by the Human Research Ethics Committees at Sir Charles Gairdner Osborne Park Hospital (RGS00065). Reciprocal approval was gained from Curtin University (HRE2017 – 0651). The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (12617001271392).

4.1.2 Participants

4.1.2.1 Inclusion criteria

Individuals were eligible to participate in the study if they: (i) were aged ≥15 years, and (ii) had a body mass index (BMI) > 16 $kg \cdot m^{-2}$. The inclusion of adolescents was because several 16 to 18 years olds begin transition to adult from paediatric clinical care.

4.1.2.2 Exclusion criteria

Exclusion criteria comprised: (i) current or recent (within the previous 4 weeks) exacerbation of CF which required oral or intravenous antibiotics; (ii) a comorbidity that would impact on their ability to undertake a maximal incremental ramp-based cycle ergometry test;

(iii) poorly controlled diabetes as deemed by their treating endocrinologist; (iv) previous lung transplant or current listing for lung transplantation; (v) participation in structured exercise at a moderate intensity two or more times per week for the previous 3 months; and (vi) the inability to provide written informed consent or follow instructions consistently due to a cognitive impairment or being unable to understand English.

4.1.3 Recruitment

Potential participants were identified and recruited from outpatient clinic appointments at the Sir Charles Gairdner Hospital (SCGH). They were provided with verbal explanation of the study, as well as a participant information and consent form summarising the study, and were given the opportunity to ask questions regarding the study. Potential participants were contacted by phone or email (mode of contact based on participant preference) within 48 hours of their clinic visit to discuss their willingness to participate. In addition to outpatient clinics at SCGH, recruitment also took place at Perth Children's Hospital (PCH), where a senior physiotherapist provided an information sheet to individuals who were potentially eligible to participate in the study. Prior to commencing participation, written informed consent was obtained from all participants, as well as from their guardian if the participant was under 18 years of age.

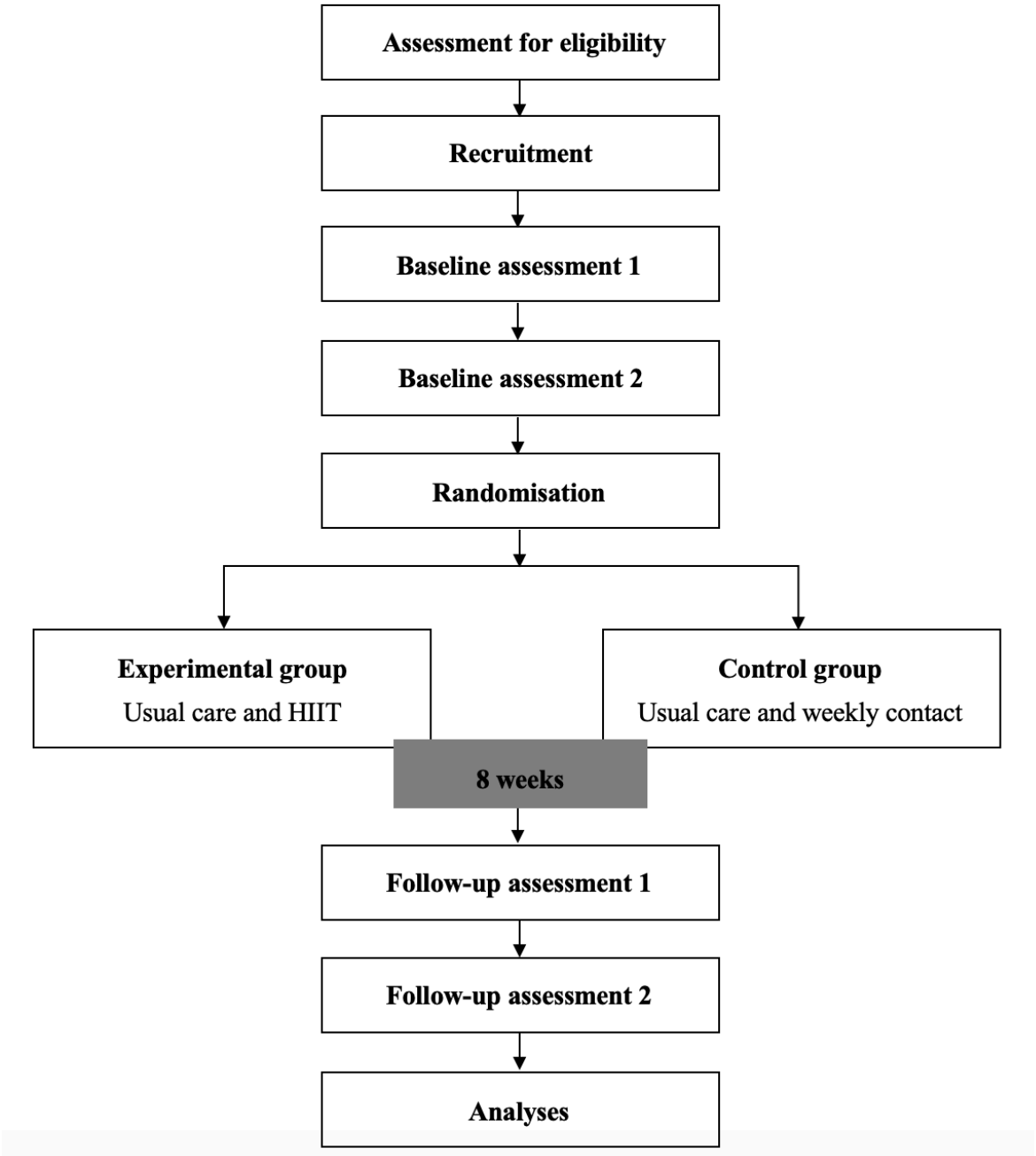


Figure 4.1 Study design flow diagram

Abbreviation: HIIT: high intensity interval training.

4.1.4 Randomisation

Participants were randomly allocated, on a 1:1 ratio, to the experimental or control group after completing the baseline assessment period. The allocation of participants was concealed using a central randomisation service (the National Health and Medical Research Council randomisation service). A minimisation algorithm was used to stratify for site of recruitment (i.e. SCGH or PCH), severity of airflow obstruction (i.e. mild: forced expiratory volume in 1 second [FEV_1] ≥ 70% predicted; moderate: FEV_1 40 to 69% predicted; or severe: FEV_1 ≤ 39% predicted) and the use (or not) of CF transmembrane conductance regulator–modifying medications.

4.1.5 Blinding and standardisation

The PhD candidate was responsible for collection of the baseline data and supervision of the HIIT sessions. The follow-up exercise assessments were conducted by respiratory scientists employed in the Department of Pulmonary Physiology at SCGH who were blinded to the participant group allocation. Study participants were instructed not to discuss their group allocation with the respiratory scientists. A number of strategies were implemented to optimise standardisation of baseline and follow-up exercise tests, including: (i) the respiratory scientists trained the PhD candidate to undertake the exercise tests in the first instance as per the departmental protocol; (ii) substantial discussion between the PhD candidate and respiratory scientists prior to study commencement in order to standardise the tests; (iii) the respiratory scientist followed a fidelity checklist for each follow-up exercise test to ensure the tests were completed in the same manner as the baseline exercise tests; and (iv) during both cycle ergometry tests, standardised instructions and verbal encouragement were provided at minute increments with the aim of facilitating a maximal effort (Appendix 3). In addition to these above-mentioned procedures, the exercise tests were quality reviewed by a member of the research team (a consultant physician with substantial experience in the area), who was not aware of or involved in the process of participant group allocation or undertaking of the HIIT sessions.

4.1.6 Assessment periods

Both baseline and follow-up assessments were completed over 2 days, separated by at least 24 hours. Each assessment visit lasted under 1.5 hours, and, where possible, both visits were completed within 2 weeks. During the baseline assessments, descriptive variables were recorded related to age, sex, height, weight and spirometry (Medgraphics USB Spirometer, MCG Diagnostics, Minnesota, USA). During baseline and follow-up assessments, in order to

evaluate the effect of the experimental intervention (i.e. HIIT), measures of exercise capacity, health-related quality of life (HRQoL), exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment were collected in both groups. To reduce the potential for participants to experience questionnaire fatigue, administration of the questionnaires was divided across the two assessment sessions. In the experimental group only, post-exercise muscle soreness (measured weekly) and tolerance (measured at every HIIT session) were measured throughout the 8-week period. The behaviour change techniques (BCTs) were mapped to Michie's BCT Taxonomy v1 [82]. At the end of the intervention period, participants in the experimental group were asked to undertake an audio-recorded semi-structured debrief interview.

4.2 Measurements

Each of the following measurement tools have been described in detail in Chapter 2 of this thesis. They are briefly described in the following section.

4.2.1 Measurements related to the primary research questions

4.2.1.1 Exercise capacity (primary outcome)

The primary measure of exercise capacity was time to symptom limitation (T_{lim}) when cycling at an intensity equal to 80% of the peak work rate (W_{peak}). In order to establish the W_{peak}, a ramp-based cycle ergometry test was undertaken on an electronically braked cycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany). Participants were asked to undertake spirometry before the test commenced. Following completion of spirometry, the exercise test commenced with 1 minute of 'rest', followed by 1 minute of unloaded cycling. Thereafter, a 'continuous ramp' protocol was used to progressively increase the work rate until the participant was unable to continue due to intolerable symptoms or volitional exhaustion (referred to as 'symptom limitation' ahead). The magnitude of change in work rate was individualised based on the participant's age and pre-existing level of fitness (reported by the participant), with the aim of achieving a test duration of between 8 and 12 minutes [164]. Throughout the test, participants were asked to cycle at a cadence of 60 revolutions per minute. Breath-by-breath measurements were collected of minute ventilation, breathing pattern, oxygen uptake (VO_2) and carbon dioxide production (VCO_2) (Medgraphics CardioO_2, Medical Graphics Corporation, Minesota, USA). Measures of heart rate (HR) and peripheral capillary oxygen saturation (SpO_2) were continuously monitored and recorded using a 12-lead electrocardiogram and an ear sensor attached to a pulse oximeter (Ohmeda Biox 3700e, Avante Health Solutions, Colorado, USA), respectively. Blood pressure (BP)

was measured every 2 minutes using an automated BP machine (Tango M2, Suntech, North Carolina, USA) with a BP cuff connected to the participant's right arm. Measures of breathlessness and muscle fatigue were recorded each minute using a modified Borg scale [329]. The test was considered to be a peak test if any of the following criteria were met at the point of test completion; (i) oxygen uptake (VO_2), work rate or HR reached ≥ 85% of the predicted values, (ii) the respiratory exchange ratio > 1.15, (iii) end-test minute ventilation (VE) exceeded the maximal voluntary ventilation (pre-test FEV_1 x 40) or, (iv) symptom scores were near maximal. The anaerobic threshold was determined non-invasively by analysing the ventilatory equivalents and the V-slope [164]. To do this, VE/VO_2 and VE/VCO_2 were plotted as a function of increasing work rate. Thereafter, anaerobic threshold was determined by examining these graphs and identifying the point at which the linearity of VCO_2 surpassed VO_2 [164].

On a separate, non-consecutive day, the constant work rate cycle ergometry test was performed. This test was conducted using identical equipment as described for the ramp-based cycle ergometry test. Participants were asked to complete a 1-minute warm-up of unloaded cycling after which the work rate was increased to 80% of the W_{peak}. An intensity of 80% of the W_{peak} was chosen as this has been demonstrated to be feasible in people with CF [325]. In addition, at this cycling intensity, more than half of people with a chronic respiratory condition (CF or chronic obstructive pulmonary disease [COPD]) achieve a T_{lim} of between 8 and 12 minutes, a test duration which is most responsive to change following the intervention period [42]. During the baseline assessment, if a participant did not demonstrate signs of symptom limitation at 10 minutes, the test was terminated and, following a seated rest of 30 minutes, the test was repeated at a higher intensity. This increase in exercise intensity was planned to ensure that the baseline test time was within the desired duration. During the follow-up assessment, the constant work rate cycle ergometry test was completed at the highest work rate used during the baseline assessment. In the follow-up assessment, the constant work rate cycle ergometry test was terminated at (and recorded as) 20 minutes for participants who had not reached symptom limitation.

On completion of both the ramp-based and constant work rate cycle ergometry tests, participants rested on the cycle ergometer for a period of 5 minutes. During this time, all measurement equipment remained in place. When the 5-minute 'recovery' period ended, participants repeated spirometry, were asked to sit in a chair, and equipment was removed.

To minimise variability during each of the exercise tests, participants were provided with written and verbal instructions to refrain from consuming caffeine or alcohol for 24 hours prior to undertaking each test, refrain from smoking in the 24 hours prior to each test, and

refrain from eating for 2 hours prior to each test. In addition, where possible, baseline and follow-up tests were scheduled to take place at a similar time of the day.

To comply with safety standards in the department, a resuscitation cart, suction equipment and a defibrillator were available in the exercise laboratory at all times during all exercise tests. All equipment outlined in this section, including the resuscitation cart, was calibrated as per the manufacturer's guidelines.

4.2.1.2 Health-related quality of life (secondary outcome)

Health-related quality of life was assessed using two questionnaires: (i) the Cystic Fibrosis Questionnaire Revised (CFQ-R) [187] and (ii) the Alfred Wellness Score for CF (AweScore-CF) [188]. The CFQ-R takes approximately 15 minutes to complete [187]. The AweScore-CF takes approximately 2 minutes [190].

4.2.1.3 Exercise self-efficacy (secondary outcome)

Exercise self-efficacy, that is, how confident a person feels towards completing exercise training, was measured using the Barriers Self-Efficacy Scale (BARSE) [194], which takes approximately 5 minutes to complete.

4.2.1.4 Feelings of anxiety and depression (secondary outcome)

Feelings of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) [204]. The HADS, which takes approximately 10 minutes to complete, has been previously used in people living with CF [207].

4.2.1.5 Exercise enjoyment (secondary outcome)

Exercise enjoyment was measured using the Physical Activity Enjoyment Scale (PACES) [330], which is a tool previously used in healthy people and which takes approximately 5 minutes to complete [331].

4.2.2 Measurements related to the secondary research questions

4.2.2.1 Post-exercise muscle soreness

Participants in the experimental group were asked if they experienced any post-exercise 'thigh' muscle soreness while completing a 'sit to stand' 24 hours following the first training session of each week. This particular muscle group was the focus of symptoms due to the

quadriceps femoris being the prime mover during cycling-based exercise. Those who reported experiencing post-exercise muscle soreness were asked to rate its severity using a 100 mm visual analogue scale (VAS) with the anchor terms 'no pain at all' to 'the worst pain ever experienced' [332]. If post-exercise muscle soreness was not experienced, the participant did not complete a VAS.

4.2.2.2 Tolerance

Participant adherence (i.e. when the participant attended a session) and completion (i.e. when the participant completed the HIIT session) were recorded throughout the intervention period. Adverse events were also monitored and recorded. These were categorised as minor if they were transient and self-limiting events (i.e. breathlessness without substantial oxygen desaturation [defined as a decrease of < 4% from the participant's pre-exercise SpO_2], muscle or general fatigue, or coughing), or major events if they required the participant to interrupt or cease a training session or necessitated medical assistance (i.e. breathlessness with important oxygen desaturation [≥ 4% from the participants pre-exercise SpO_2], pain, vasovagal events or haemoptysis).

4.2.2.3 Debrief interviews

Participants allocated to the experimental group of the RCT were invited to undertake a semi-structured interview (debrief) upon completion of the intervention period. Each interview was designed to take approximately 20 to 30 minutes. All interview sessions were facilitated by the PhD candidate, and audio-recorded to allow for (de-identified) transcription. Participants were permitted to choose whether interviews were undertaken at their home, in the community or during scheduled outpatient clinic visits at SCGH to minimise the associated time and travel burden. The interview scripts were semi-structured.

The interview script was designed to understand participant perspectives on the HIIT program. Open-ended questions were used to guide the sessions, with the PhD candidate permitted to adapt the questioning as required. The script was as follows:

1. Now that you have completed the HIIT program, are you able to tell me about your experience?
2. When you think about the program, what factors facilitated or enabled your participation (in the HIIT)?
3. Were there any barriers or limitations to your participation in the program? What were the most difficult parts (in the HIIT)?
4. Can you describe how your body felt during the HIIT program?

5. Was there anything you would have changed/altered about the HIIT program? What would you have changed about the program?
6. What affect did the HIIT program have on your routine? How much did the training affect your routine?
7. How do you feel about incorporating HIIT into your weekly routine? What about the HIIT program would you be able to incorporate into your daily routine?

4.3 Intervention period

Regardless of group allocation, participants were asked to continue with their usual care throughout the duration of the study. This included medication, nutritional support, airway clearance regimens and attendance at a multidisciplinary outpatient CF clinic, which occurs quarterly or more frequently if clinically indicated. Any changes to the participant's usual treatment routine was recorded on a weekly basis.

4.3.1 Experimental group

Each training session involved a 2-minute 'warm-up', followed by a 30-second 'work' phase and 30-second 'rest' period, with this 1-minute cycle repeated six times. The work to rest periods were followed by a 2-minute 'cool-down' period. Therefore, the total training time per session, inclusive of rest periods, was 10 minutes. A physiotherapist (the PhD candidate) who is trained in the management of people with CF was present for each session. The specific role of the physiotherapist throughout each session is discussed in Part 2 of Chapter 7. To minimise the onset of post-exercise muscle soreness and optimise adherence, the training program commenced with a 'lead-in' phase which involved only two sessions of HIIT in weeks 1 and 2. Subsequent weeks (3 to 8 inclusive) comprised thrice-weekly HIIT. The training intensity was prescribed using measurements of W_{peak} achieved during the ramp-based cycle ergometry test completed during the baseline assessments. Specifically, the first training session was prescribed at 60% W_{peak} with the goal of achieving a training intensity equal to 80% of W_{peak} during the fourth training session (i.e. the end of week 2). Thereafter, training intensity was increased as rapidly as symptoms of breathlessness and muscle fatigue permitted. Training was completed at one of two sites (either SCGH or Osbourne Park Hospital), and the participant was permitted to choose the site that was most convenient for them. The model of exercise bike used for the HIIT sessions was identical at both training sites (Orbit Eco Generator Interval Bike OEB2002, Orbit, Perth, Australia). Measures of HR and SpO_2 were monitored using an oximeter and finger sensor (Masimo SET Rad-5, Masimo, California, USA) [333] throughout HIIT sessions. The individual HIIT sessions were audio-recorded.

If a participant in the experimental group reported the onset of symptoms indicative of an exacerbation of CF (i.e. increased sputum volume, changes in the characteristics of sputum, haemoptysis, increased cough, pain from coughing, new wheeze or increased wheeze, new or increased chest tightness, shortness of breath or difficulty breathing, increased fatigue or lethargy, fever, loss of appetite or weight, sinus pain or tenderness), they were referred to the CF team for medical review. If an exacerbation was diagnosed by the treating CF team, the participant was invited to continue participating in HIIT sessions once deemed to be medically stable by a CF clinician. In the event of missed attendance to HIIT sessions, the training program was extended by a maximum of 2 weeks so that the participant had 10 weeks to complete the 22 HIIT sessions.

Stringent hand hygiene and cleaning procedures were adhered to at all times to reduce the risk of cross-contamination between participants [114]. Hard surfaces of the exercise room were cleaned using hospital-grade cleaning wipes. In addition, participants allocated to the experimental group who had differing respiratory pathogens were not permitted to use the exercise room within 24 hours of each other.

4.3.2 Control group

Participants allocated to the control group were contacted once a week by the PhD candidate to discuss changes to their symptoms, healthcare utilisation (i.e. contact with the CF team and attendance at the CF clinic which was outside of the normal frequency), and participation in exercise over the preceding week. Participants were allowed to choose the way in which this contact was made: phone calls, SMS or emails. Regardless of which method of contact was chosen by the participant, the questions were standardised, and interaction between the investigator and participant was designed to take under 5 minutes per week in order to minimise disruption to the participant's routine. If a participant allocated to the control group reported any symptoms that were suggestive of an exacerbation, they were referred to the CF team for medical review.

4.4 Data management and statistical analysis

The results of this study were analysed according to the intention-to-treat principle [334, 335] using STATA (version 15, StataCorp, Texas, USA) and the analysis plan was developed in consultation with a biostatistician. Where possible, in keeping with current recommendations, differences and 95% confidence intervals around the differences were planned to be reported, rather than probability (p) values alone [336].

The magnitude of change from baseline to follow-up between the two groups was analysed using the rank-sum (Mann-Whitney U) test and reported using p values [337-339]. The 95% confidence intervals of the median were used to analyse differences within groups from baseline to follow-up [340]. As this technique is uncommonly used, within-group analysis was cross-checked using signed-rank tests with p values provided. The original analysis was undertaken without imputation of missing data. For completeness, in the event of missing data, a secondary analysis with baseline observation carried forward was undertaken, results of which are given in Appendix 4.

Measurements of exercise capacity during the baseline and follow-up assessment period are presented as end-exercise values unless stated otherwise. For the constant work rate cycle ergometry test, data are presented at end-exercise and at isotime. Isotime refers to the measures achieved during the shortest constant work rate cycle ergometry test, correlated with measures at the same time-point on the alternative test. Where participants achieved a shorter exercise time during the follow-up test, this test was substituted with the baseline value.

For the proportion of participants who developed post-exercise muscle soreness, the severity of this symptom over the 8-week intervention period, and tolerance (attendance and completion) of the HIIT program were expressed as median and interquartile range unless otherwise stated.

Data obtained through audio-recorded HIIT sessions and debrief interviews were analysed using Nvivo software (version 12, QSR International Pty Ltd, Massachusetts, USA). The audio-recordings were uploaded onto the platform, and then transcribed verbatim by the PhD candidate. Transcripts were then coded and evaluated for common themes by the PhD candidate.

4.4.1 Sample size calculations

The primary measure for this RCT was exercise tolerance. There are several protocols available to assess this construct in people with a chronic respiratory condition. However, earlier work suggests that measures of submaximal exercise capacity (i.e. endurance) are more responsive to change than peak measures of exercise capacity. In a sample of 15 young adults with CF, the coefficient of variation (within-subject over time) for T_{lim} for a constant work rate cycle ergometry test performed at 80% of W_{peak} was 6% (similar to that for FEV_1) [170]. For these reasons, the sample size calculation for this study was based on the

measurements of T_{lim} during a constant work rate cycle ergometry test, conducted at 80% of W_{peak}.

There is limited information pertaining to the minimal clinically important difference (MCID) for the T_{lim} in people with CF. However, in people with COPD, the MCID has been proposed to be 100 seconds. In people with CF (n = 8, mean ± standard deviation [SD], aged 26 ± 1 years), who have similar severity of lung disease as those who were recruited to the study described in the study conducted in this program of research (FEV_1 ranged from 20 to 61% predicted), the T_{lim} during a constant power test performed at 80% of W_{peak} on room air was 673 ± 63 seconds and this increased to 835 ± 99 seconds when the same test was performed on supplemental oxygen [325]. Using these data, in order to detect a between-group difference of 100 seconds (MCID for T_{lim} in COPD), with a SD of 99 seconds (largest of the two SDs reported for T_{lim} in a CF population similar to that targeted in the current RCT, $\alpha = 0.05$ and $1-\beta = 0.8$), a sample size of 16 per arm (n = 32 in total) was required. This sample size was inflated by 20% to account for possible loss to follow-up. Therefore, the recruitment target for this study was 40.

A sample size of 16 per arm would provide adequate power to detect a between-group difference in the 'gold-standard' measure of peak exercise capacity, VO_{2peak}, of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ with a SD of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$.

CHAPTER 5

PHYSIOLOGICAL AND SYMPTOM RESPONSES TO LABORATORY-BASED EXERCISE TESTING

Overview

Chapter 5 presents an opportunistic analysis of baseline data collected for use in the randomised controlled trial (RCT) (described in Chapter 4). The results of these analyses explore differences in responses to two different laboratory-based exercise tests: a maximal incremental ramp-based cycle ergometry test and a constant work rate cycle ergometry test in adults with CF. This opportunistic analysis helped to support the choice of conducting the constant work rate cycle ergometry test at 80% of the peak work rate (W_{peak}). A condensed version of these analyses was submitted for publication as a brief report in February 2020. The full assessment protocol and measurements made for the RCT can be found in Chapter 4 and have been published in a peer-reviewed journal [61]. The main results of the RCT are provided in Chapter 6.

5.1 Aims

The purpose of this study was to: (i) compare the physiological and symptom responses during and for 5 minutes following a constant work rate cycle ergometry test to those elicited

during a ramp-based cycle ergometry test; and (ii) determine the limits of agreement for physiological measures of exercise capacity collected on test completion, in adults with CF.

5.2 Study design

The methods used to collect the data presented in the chapter have been described in Chapter 4 and published in a peer-reviewed journal [61]. Briefly, data collection took place between October 2017 and October 2019. People with CF were invited to participate in this study if they: (i) were aged ≥15 years, and (ii) had a body mass index (BMI) > 16 $kg \cdot m^{-2}$. Exclusion criteria comprised: (i) current or recent (within the previous 4 weeks) exacerbation of CF requiring antibiotics; (ii) a comorbidity that would impact on their ability to undertake a peak exercise test; (iii) poorly controlled diabetes; (iv) previous lung transplant or current listing for lung transplantation; (v) participation in structured exercise at a moderate intensity two or more times per week for the previous 3 months; and (vi) inability to provide written informed consent. People with CF were identified from scheduled outpatient clinic appointments at the Sir Charles Gairdner Hospital and Perth Children's Hospital CF centres, provided with an information sheet, and contacted by phone call within 48 hours to discuss their willingness to participate. Written informed consent was obtained from all participants. After providing written informed consent, participants completed an assessment period, which took place across two assessment days, separated by at least 24 hours. Measurements were taken of exercise capacity (in a ramp-based cycle ergometry test and a constant work rate cycle ergometry test). The recruitment target (n = 40) determined for the RCT of this program of research was applied to the Chapter 5.

5.3 Measurements

Information regarding all measurements collected in the RCT have been described in Chapter 4. Details for each of the measurements relevant specifically to the analyses conducted in this chapter are provided briefly below.

5.3.1 Anthropometric data, respiratory function and medical history

To describe the participant group, anthropometric and demographic data (age, height, weight, sex), and measurements of respiratory function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio) were recorded. Details of comorbidities were collected following a review of participants' medical records.

5.3.2 Exercise capacity

A ramp-based cycle ergometry test was undertaken on an electronically braked cycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany). The test commenced with 1 minute of 'rest', followed by 1 minute of unloaded cycling. Thereafter, a 'continuous ramp' protocol was used to progressively increase the work rate until the participant was unable to continue due to intolerable symptoms (i.e. symptom limitation). The magnitude of change in work rate per minute (10 to 25 W) was individualised based on the participant's age and pre-existing level of fitness (as reported by the participant), with the aim of achieving a test duration of between 8 and 12 minutes [164]. Throughout the test, participants were asked to cycle at a cadence of 60 revolutions per minute. Breath-by-breath measurements were collected of minute ventilation, breathing pattern, oxygen uptake (VO_2) and carbon dioxide production (VCO_2) (Medgraphics CardioO2, Medical Graphics Corporation, Minnesota, USA). Measures of heart rate (HR) and peripheral capillary oxygen saturation (SpO_2) were continuously monitored and recorded using a 12-lead electrocardiogram and an ear sensor attached to a pulse oximeter (Ohmeda Biox 3700e ear sensor, Biox Technology, Colorado, USA), respectively. Blood pressure (BP) was measured every 2 minutes using an automated BP machine (Tango M2; Suntech, North Carolina, USA) with a BP cuff connected to the participant's right arm. Measures of breathlessness and muscle fatigue were recorded each minute using a modified Borg scale [329]. The test was considered to be a peak test if any of the following criteria were met at the point of test completion; (i) oxygen uptake (VO_2), work rate or HR reached ≥ 85% of the predicted values, (ii) the respiratory exchange ratio > 1.15, (iii) end-test minute ventilation (VE) exceeded the maximal voluntary ventilation (pre-test FEV_1 x 40) or, (iv) symptom scores were near maximal. The anaerobic threshold was determined non-invasively by analysing the ventilatory equivalents and the V-slope [164]. To do this, VE/VO_2 and VE/VCO_2 were plotted as a function of increasing work rate. Thereafter, anaerobic threshold was determined by examining these graphs and identifying the point at which the linearity of VCO_2 surpassed VO_2 [164].

On a separate, non-consecutive day, the constant work rate cycle ergometry test was performed. This test was conducted using identical equipment as described for the ramp-based cycle ergometry test. Participants were asked to complete a 1-minute warm-up of unloaded cycling after which the work rate was increased to 80% of the W_{peak}. Following both tests, recovery data were collected for a period of 5 minutes.

5.4 Statistical analysis

Statistical analysis was performed using STATA (version 15, StataCorp, Texas, USA). The results are presented as median [interquartile range; IQR]. Between-test differences are expressed as median difference and 95% confidence interval (CI) [341]. These Cis can be interpreted in the same manner as usual. However, the limits are not necessarily symmetrical around the sample estimate of the median difference. Bland–Altman plots [342] were used to present the bias and limits of agreement (±1.96 × standard deviation of the differences) in VO_{2peak}, peak minute ventilation (V_{Epeak}) and maximal heart rate (HR_{max}) achieved during the two tests.

5.5 Results

5.5.1 Recruitment and participation

At the commencement of the study, there were 180 people under the care of the CF centre at Sir Charles Gairdner Hospital (SCGH). Forty-one (23%) were ineligible to participate as they either lived outside the Perth metropolitan area (n = 40) or were unable to read and understand English (n = 1). Of the remaining participants (n = 139), 128 declined to participate. Reasons cited for non-participation included: not willing to travel to SCGH or Osborne Park Hospital for testing or intervention sessions (n = 59); ongoing medical issues limiting participation, including respiratory exacerbation (n = 29); already exercising at least twice per week (n = 14); and being time-poor or ‘too busy’, or having a work schedule that did not permit participation in the study (n = 7). Four potential participants declined, but did not give a specific reason. A further nine potential participants expressed interest in the study and were provided with a participant information and consent form, but did not respond to phone messages, SMS and/or emails following the clinic visit to further discuss participation in the study. Two potential participants who were colonised with nontuberculous mycobacteria expressed interest in the study, but were not permitted to take part due to the risk of cross-infection in the exercise laboratory.

Fourteen participants were eligible and willing to participate in the study. As this analysis of baseline data forms part of an RCT, data related to the recruitment and participation of participants will be thoroughly outlined in the next chapter (Chapter 6).

5.5.2 Anthropometric data, respiratory function and medical history

The anthropometrics, spirometry results and the relevant comorbidities of participants are presented in Table 5.1. Of the 14 participants who agreed to participate in the study, five were characterised by a mild airflow obstruction (i.e. $FEV_1 \geq 70\%$ predicted), seven were characterised by a moderate airflow obstruction (FEV_1 40 to 69% predicted), and two by a severe airflow obstruction ($FEV_1 \leq 39\%$ predicted). Six (43%) of the participants were female. Body mass index ($kg \cdot m^{-2}$) of the participants ranged from 18.9 $kg \cdot m^{-2}$ (classified as borderline underweight) to 36.4 $kg \cdot m^{-2}$ (classified as obese) [343]. In the year preceding participation in the study, nine participants had no admissions (64%), two participants had one admission (14%), two had two admissions (14%) and one participant had five admissions (7%).

Of the participants who entered the study and completed the baseline assessment period, genotypes included *F508del* homozygous (n = 8), *G551D/F508del* heterozygous (n = 1), *W1282X* homozygous (n = 1), *G542X/2789/5G>A* (n = 1), *Delta F508/F1066h* (n = 1) and *C3909C>G/4004T>C* (n = 1). The genotype of one participant was not listed in the medical records.

The participants who entered the study were prescribed the following medications by their respiratory specialist: hypertonic saline (n = 11), dornase alpha (n = 13), tobramycin podhaler (n = 5), vitamin supplements (Vitamin ABDECK) (n = 11), azithromycin (n = 7), salbutamol (n = 12), pancreatic enzymes (n = 9), and fluticasone and/or gene-modifying medications (n = 5).

Of the 14 participants, 43% were employed on a full-time basis (n = 6), 36% were employed on a part-time basis (n = 5), 14% were students (n = 2) and one participant (14%) was on parental leave.

Table 5.1 Anthropometrics, respiratory function and comorbidities of study participants

Variable	Total sample (n = 14)	
Age (yr)	31 [28, 35]	
Height (cm)	176 [163, 182]	
Sex (n female [%])	6 [43]	
Weight (kg)	76 [64, 92]	
FEV_1 (L)	2.20 [1.74, 3.40]	
FEV_1 (% predicted)	61 [45, 80]	
FVC (L)	3.35 [3.07, 5.17]	
FVC (% predicted)	82 [64, 95]	
FEV_1/FVC	0.7 [0.6, 0.7]	
Comorbidity	**n**	**%**
Asthma	2	14
CFRD	4	29
CF-related liver disease	2	14
Cholelithiasis	2	14
Ileus	1	7
OSA	1	7
Osteopenia	3	21
Pancreatic insufficiency	10	71
Reflux	4	29

Data are presented as median [IQR] unless otherwise stated. Abbreviations: CF: cystic fibrosis, CFRD: cystic fibrosis–related diabetes, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, IQR: interquartile range, OSA: obstructive sleep apnoea.

5.5.3 Exercise capacity

The results of the ramp-based and constant work rate cycle ergometry tests are shown in Table 5.2 and Table 5.3, respectively.

Table 5.2 Results of ramp-based cycle ergometry test

Variable	Total sample (n = 14)
VO_{2peak} ($L \cdot min^{-1}$)	2.1 [1.6, 2.4]
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	28 [22, 32]
VO_{2peak} (% predicted)	76 [66, 93]
VCO_2 ($L \cdot min^{-1}$)	2.5 [2.1, 3.3]
Increment (Watts)	20 [15, 25]
W_{peak} (Watts)	180 [122, 223]
W_{peak} (% predicted)	85 [78, 90]
RER	1.3 [1.2, 1.3]
V_{Epeak} ($L \cdot min^{-1}$)	67 [60, 98]
End-test breathlessness	7 [5, 8]
End-test leg muscle fatigue	9 [8, 9]
Resting SpO_2 (%)	97 [95, 97]
Nadir SpO_2 (%)	93 [92, 94]
HR_{max} (bpm)	163 [159, 172]
HR_{max} (% predicted)	88 [85, 93]
End-test RR ($breaths \cdot min^{-1}$)	43 [33, 48]
O_2 pulse	12 [10, 15]
AT (% VO_{2peak})	41 [32, 48]
Test duration (s)	539 [487, 562]

Data are presented as median [IQR] unless otherwise stated. Abbreviations: AT: anaerobic threshold, bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, O_2 pulse: oxygen pulse, RER: respiratory exchange ratio, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, VCO_2: carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake, W_{peak}: peak work rate. End-test symptoms measured using the Borg scale (0 to 10). 'Increment' represents the magnitude of change each minute (Watts).

Table 5.3 Results of constant work rate cycle ergometry test

Variable	Total sample (n = 14)
T_{lim} (s)	252 [222, 306]
VO_{2peak} ($L \cdot min^{-1}$)	1.9 [1.5, 2.4]
VO_{2peak} (% predicted)	70 [65, 97]
VCO_{2peak} ($L \cdot min^{-1}$)	2.5 [1.8, 2.9]
V_{Epeak} ($L \cdot min^{-1}$)	65 [56, 98]
End-test breathlessness	7 [5, 8]
End-test leg muscle fatigue	9 [6, 9]
Resting SpO_2 (%)	97 [97, 98]
Nadir SpO_2 (%)	95 [91, 97]
HR_{max} (bpm)	160 [148, 167]
End-test RR ($breaths \cdot min^{-1}$)	42 [30, 44]

Data are presented as median [IQR] unless otherwise stated. Abbreviations: bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, T_{lim}: time to symptom limitation, VCO_2: rate of carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake. End-test symptoms measured using the Borg scale (0 to 10).

5.5.3.1 Comparison between responses during the two exercise tests

A comparison of responses to the ramp-based and constant work rate cycle ergometry tests is available in Table 5.4. Test duration was shorter in the constant work rate cycle ergometry test (median difference [95% CI] 288 [241 to 304]). There were no other differences in other measures between the two tests.

Table 5.4 Comparison between the ramp-based and constant work rate cycle ergometry tests

Variable	Ramp-based cycle ergometry (n = 14)	Constant work rate cycle ergometry (n = 14)	Median difference (95% CI)
Test duration (s)	539 [488, 561]	252 [226, 305]	288 (241 to 304)
W_{peak} (Watts)	180 [125, 219]	144 [101, 177]	N/A
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	28 [22, 31]	27 [21, 32]	1 (−1 to 2)
VO_{2peak} (% predicted)	76 [66, 93]	70 [65, 97]	4 (−3 to 7)
HR_{max} (bpm)	163 [159, 172]	160 [148, 167]	6 (−3 to 11)
HR_{max} (% predicted)	88 [84, 93]	84 [80, 87]	3 (2 to 5)
Nadir SpO_2 (%)	93 [92, 94]	95 [91, 97]	−1 (−2 to 2)
End-test RR ($breaths \cdot min^{-1}$)	43 [33, 48]	42 [30, 44]	2 (−1 to 7)
End-test breathlessness	7 [5, 8]	7 [5, 8]	0 (−3 to 1)
End-test leg muscle fatigue	9 [8, 9]	9 [6, 9]	2 (−0.2 to 4)

Data are presented as median [IQR] and the median difference (95% CI). Abbreviations: bpm: beats per minute, CI: confidence interval, HR_{max}: maximal heart rate (calculated as 220–age) [344], IQR: interquartile range, N/A: not appropriate, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, VO_{2peak}: peak rate of oxygen uptake [345], W_{peak}: peak work rate. End-test symptoms measured using the Borg scale (0 to 10).

5.5.3.2 Agreement between exercise measures

The individual agreement between measures of VO_{2peak}, V_{Epeak} and HR_{max} collected during the ramp-based and constant work rate cycle ergometry tests are presented in Bland–Altman plots (Figure 5.1).

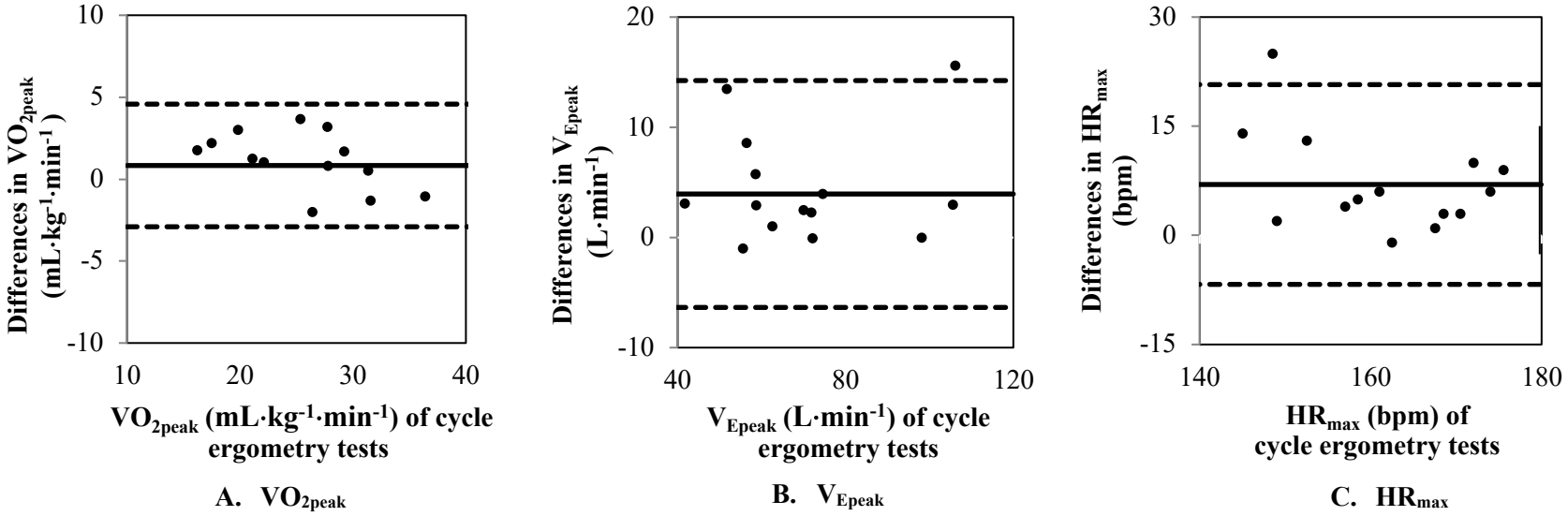


Figure 5.1 Bland–Altman analysis for the difference between the ramp-based and constant work rate cycle ergometry tests for the peak rate of oxygen uptake (A), peak minute ventilation (B) and maximal heart rate (C)

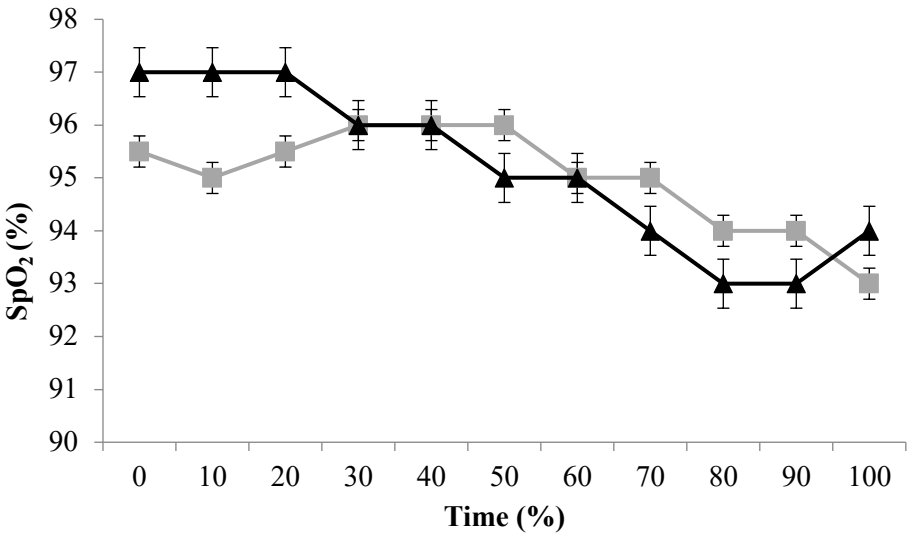
Y axis values: difference in measures calculated as ramp-based minus constant work rate cycle ergometry test values. X axis values: values averaged between ramp-based and constant work rate cycle ergometry tests. Black line indicates bias and dashed lines indicate limits of agreement (±1.96 SD).

Abbreviations: bpm: beats per minute, HR_{max}: maximal heart rate, SD: standard deviation, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake.

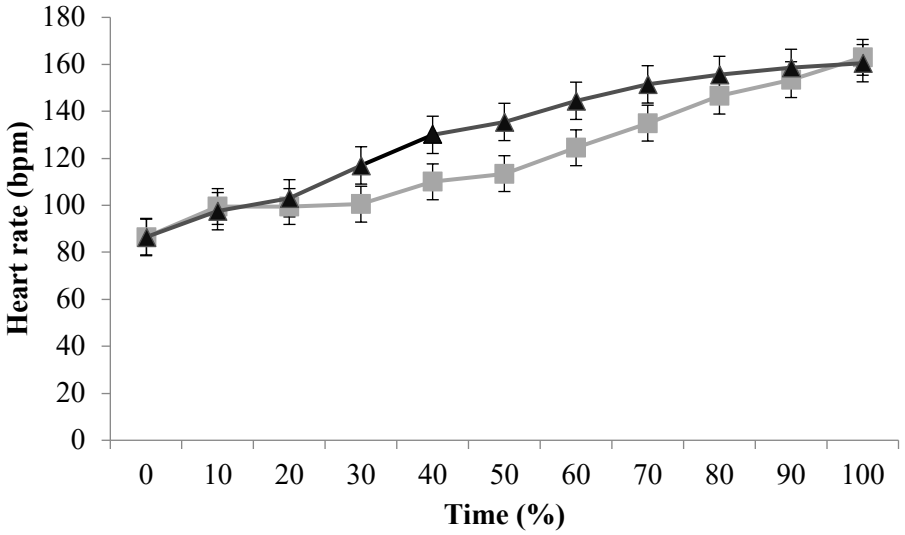
5.5.3.3 Patterns of exercise response

Figure 5.2 demonstrates the patterns of change in SpO_2, HR and VO_2 between the two exercise tests. Peripheral capillary oxygen saturation declined in a more linear manner for the constant work rate cycle ergometry test compared to the ramp-based cycle ergometry test. Heart rate increased linearly for both exercise tests. Peripheral capillary oxygen saturation decreased from median [IQR] 96% [94, 96] (resting) to 93% [92, 94] (peak) in the ramp-based cycle ergometry test, and from 97% [96, 97] (resting) to 94% [91, 95] (peak) in the constant work rate cycle ergometry test. Heart rate increased from 87 bpm [79, 96] (resting) to 163 bpm [160, 172] (peak) during the ramp-based cycle ergometry test, and from 87 bpm [78, 94] (resting) to 161 bpm [151, 167] (peak) in the constant work rate cycle ergometry test.

(a)


98
97
96
95
94
93
92
91
90
SpO2 (%)
0
10
20
30
40
50
60
70
80
90
100
Time (%)

(b)


180
160
140
120
100
80
60
40
20
0
Heart rate (bpm)
0
10
20
30
40
50
60
70
80
90
100
Time (%)

c)

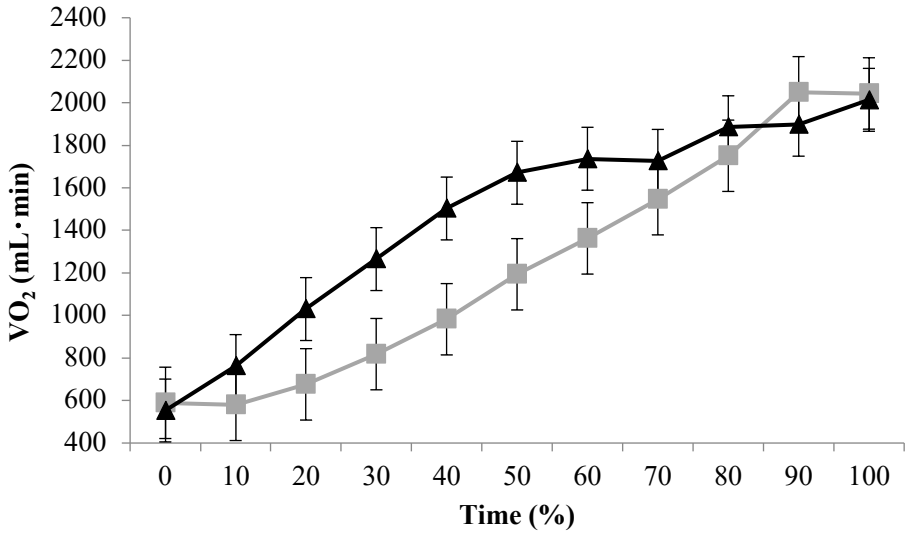


Figure 5.2 Comparison of patterns of response of (a) oxygen saturation (b) heart rate and (c) oxygen uptake during the ramp-based and constant work rate cycle ergometry tests

Data are presented as median and standard error. Data are available for all participants (n = 14). '■' represent ramp-based cycle ergometry test data. '▲' represent constant work rate cycle ergometry test data. Time is represented in epochs equivalent to 10% of overall test duration.

Abbreviations: bpm: beats per minute, SpO_2: peripheral capillary oxygen saturation, VO_2: oxygen uptake.

5.5.3.4 Symptom response

Fatigue was the most commonly reported limiting symptom in 11 (79%) and 10 (71%) participants for the ramp-based and constant work rate cycle ergometry tests, respectively. Breathlessness was the other predominant limiting symptom, reported in two (14%) and three (21%) participants for the ramp-based and constant work rate cycle ergometry tests, respectively. One participant (7%) reported the severity of their leg fatigue and dyspnoea to be equal at test cessation.

5.5.3.5 Heart rate recovery

Five-minute HR recovery was comparable between the two exercise tests. Table 5.5 presents the HR recovery data and Figure 5.3 illustrates the pattern of HR recovery (median scores) for each exercise test. There was no difference in the resting HR (median difference 10 bpm, 95% CI −1 to 15) or the magnitude of HR recovery at 5 minutes (median difference 10 bpm, 95% CI −1 to 15) between the two exercise tests. In addition, the pattern of recovery was similar.

Table 5.5 Heart rate recovery

Variable	Total sample
Ramp-based	
HR_{max} (bpm)	163 [159, 172]
HR at 1 minute (bpm)	150 [145, 158]
HR at 1 minute (% HR achieved)	90 [88, 92]
HR at 5 minutes (bpm)	118 [112, 125]
HR at 5 minutes (% HR achieved)	71 [68, 74]
Constant work rate	
HR_{max} (bpm)	160 [148, 167]
HR at 1 minute (bpm)	139 [135, 150]
HR at 1 minute (% HR achieved)	87 [85, 89]
HR at 5 minutes (bpm)	112 [105, 117]
HR at 5 minutes (% HR achieved)	70 [68, 71]

Data are presented as median [IQR] unless otherwise stated. Data available for 13 participants (ramp-based) and 12 participants (constant work rate). Abbreviations: bpm: beats per minute, HR: heart rate, HR_{max}: maximal heart rate, IQR: interquartile range.

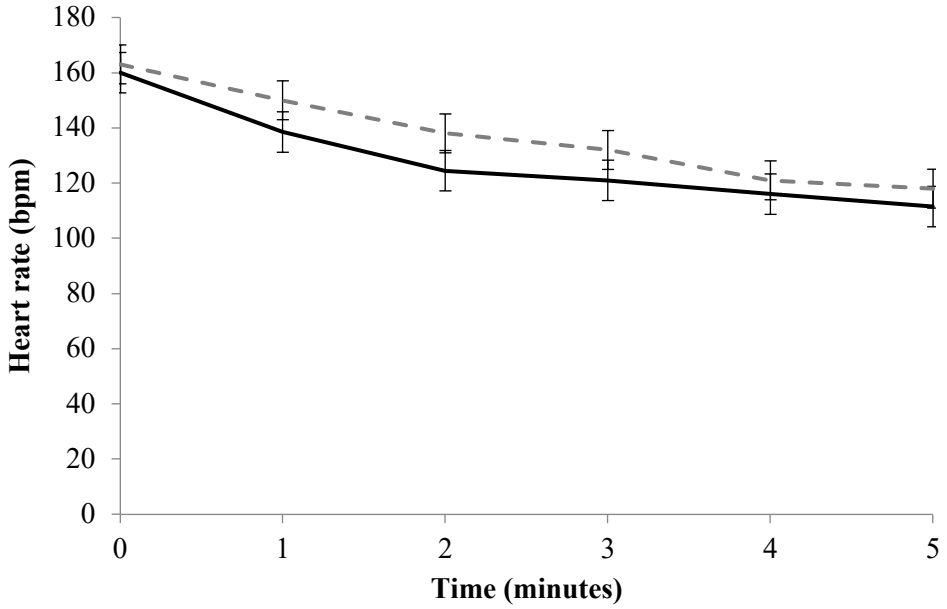


Figure 5.3 Line graph comparing 5-minute heart rate recovery (%) following each exercise test

Data are presented as heart rate recovery pattern (median values with standard error) per minute for the ramp-based (- - -) and constant work rate (—) cycle ergometry tests.

Abbreviation: bpm: beats per minute.

5.6 Discussion

This study aimed to: (i) compare the physiological and symptom responses during and for 5 minutes following a constant work rate cycle ergometry test performed at 80% of the W_{peak} to those elicited during a ramp-based cycle ergometry test; and (ii) determine the limits of agreement for physiological measures of exercise capacity collected on test completion, in adults with CF. The main findings of this study were that the constant work rate cycle ergometry test elicited peak physiological and symptom responses, despite being shorter in duration than the ramp-based test. Other constant work rate tests have been investigated in people with CF (i.e. supramaximal verification following a maximal incremental cycle ergometry test at ~100-110% of the W_{peak}) [350]. However, trivial differences demonstrated in the end-test exercise responses between a ramp-based and constant work rate cycle ergometry test, when conducted at 80% of the W_{peak}, is a novel finding in this population. Similar data have previously been reported in people with chronic obstructive pulmonary disease (COPD) [346] and pulmonary arterial hypertension (PAH) [347]. Studies on PAH have demonstrated similar results to this study for VO_{2peak}, ventilation, HR_{max}, SpO_2 and symptoms, despite the constant workload in the latter study being set at 75% of the W_{peak} [347].

Bland–Altman plots demonstrated that the differences between the two tests in measures of VO_{2peak}, V_{Epeak} and HR_{max} were not systematic. The limits of agreement can be used to help interpret individual responses. That is, for any individual, when the magnitude of change in VO_{2peak}, V_{Epeak} and HR_{max} exceeds their respective limit of agreement, we can be 95% confident that the difference was not simply due to the error associated with using a different protocol on a different day. In addition, HR recovery following both tests was comparable.

In this program of research, a workload of 80% of the W_{peak} was chosen for the constant work rate cycle ergometry tests due to the documented reproducibility of testing at this intensity [170], and the investigators' intention for the test to be conducted well above the anaerobic threshold and critical power (without formally measuring critical power) [348]. The median T_{lim} for the constant work rate test of 252 seconds [222, 306] was within the recommended timeframe of 180 to 480 seconds for a baseline test, suggesting that the prescribed work rates were likely to be above the critical power as anticipated [348].

Laboratory-based exercise tests, including the ramp-based and constant work rate cycle ergometry tests, are useful methods of measuring exercise capacity, demonstrating minimal variability within-person in chronic respiratory populations, including people living with CF [42, 164, 349]. In a sample of young adults with CF, the coefficient of variation (within-

subject over time) for T_{lim} during a constant work rate cycle ergometry test done at 80% of W_{peak} was 6% (similar to that for FEV_1) [170].

The measurement of exercise capacity is fundamental in the management of people with CF for numerous reasons, including to determine the cause of exercise limitation, measure changes in exercise capacity (over time or in response to an intervention), to serve as 'proxy' markers of survival [38], and to optimally prescribe exercise interventions. Maximal incremental cardiopulmonary exercise tests (CPETs) in people with chronic respiratory conditions, including CF, have screening and diagnostic value, particularly for the evaluation of unexplained symptoms, which may not be elicited or accurately recorded during field-based exercise tests. Maximal incremental ramp-based cycle ergometry tests are the most commonly used CPET clinically and in research to measure maximal or peak exercise capacity [162]. These tests are regarded as a valid and reliable 'gold-standard' measure to assess markers of exercise capacity [164]. In addition to the diagnostic value, ramp-based cycle ergometry tests are required to accurately establish the workload at which to set a constant work rate cycle ergometry test. Despite the need for ramp-based tests, constant work rate cycle ergometry tests, which are currently seldom used in people with CF, may have important value in research and clinical practice. Constant work rate tests have been used in other chronic cardiorespiratory populations, such as COPD and PAH. Time to symptom limitation, also known as T_{lim}, is a sensitive measure to detect change in exercise tolerance. In addition to the sensitivity of T_{lim}, the intensity at which constant work rate tests are performed is likely to be more comparable to the intensity that people with CF (and other chronic respiratory conditions) may achieve during exercise training completed in daily life, making the results of this test meaningful.

Data from this study provides evidence that constant work rate cycle ergometry tests elicit peak physiological and symptom responses similar to those of a ramp-based cycle ergometry test in adults with CF. Considering these data, in practice, clinicians should be mindful of the intensity and length of prescribed exercise training, and the level of initial therapist supervision and patient monitoring provided in non-laboratory-based settings.

5.6.1 Limitations

The results of this study would be strengthened by recruiting a larger sample of participants. Had this study been conducted as a standalone study (i.e. not as a component of an RCT), it is possible that a greater number of participants would have enrolled.

Since the planning of this program of research, ramp-based cycle ergometry tests with supramaximal verification have gained momentum as a method to confirm results of VO_{2peak}, among other important measures of cardiorespiratory fitness and performance. These tests are likely to be a superior approach to measuring cardiorespiratory fitness in future research, compared to testing without supramaximal verification [163, 350]. The novel nature of the constant work rate cycle ergometry test is acknowledged by the PhD candidate.

There are a number of limitations to undertaking laboratory-based CPETs in clinical practice for people with CF. These include their cost, time and personnel-intensive nature, and space requirements. As such, the uptake of these tests in CF centres is limited [40, 41, 162].

5.7 Summary

In adults with CF, this is the first study to demonstrate trivial differences in the end-test exercise responses between ramp-based and constant work rate cycle ergometry tests. The limits of agreement can be used to help interpret individual responses. Although the constant work rate test was shorter in duration, it elicited similar peak responses to the ramp-based test. The results of this study provide evidence that the constant work rate cycle ergometry test, when conducted at 80% of the W_{peak}, elicits peak physiological and symptom responses. The median T_{lim} for the constant work rate test was within the recommended timeframe of 180 to 480 seconds (or 3 to 8 minutes) for a baseline test, indicating that the prescribed work rates were likely to be markedly above the critical power [348]. Therefore, for clinicians prescribing exercise at an intensity approaching or equivalent to 80% of the W_{peak} in a non-laboratory-based setting, the presence of a therapist and monitoring of physiological response should be considered, particularly during the initial stages of exercise prescription and progression of exercise intensity.

CHAPTER 6

EFFECTS OF HIGH INTENSITY INTERVAL TRAINING ON EXERCISE CAPACITY IN PEOPLE WITH CYSTIC FIBROSIS: A RANDOMISED CONTROLLED TRIAL

Overview

This chapter presents the results and discussion sections of the prospective, single-blinded randomised controlled trial (RCT). The methods for this study were described in Chapter 4 and published in a peer-reviewed journal [61].

The specific research question answered in this chapter was: in people with cystic fibrosis (CF), what was the effect of an 8-week low-volume high intensity interval training (HIIT) program, compared with weekly contact and no formal exercise training, on exercise capacity (primary outcome), health-related quality of life (HRQoL), exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment (secondary outcomes)?

Secondary research questions also answered were: in people with CF who were allocated to the experimental group of the RCT, (i) what proportion of participants developed post-exercise quadriceps femoris muscle soreness each week during the 8-week HIIT program, and how severe was this symptom; (ii) how well did the participants tolerate the HIIT program; and (iii) what were the participants' reflections on the 'facilitators' and 'barriers' following the HIIT program?

6.1 Results

The results are presented in three sections. The first section describes participant recruitment and participation, and the characteristics of the experimental and control groups (6.1.1 and 6.1.2). The second section (6.2) presents data pertaining to the primary research question. The third section (6.3) presents data pertaining to the secondary research questions, and debrief interviews conducted following the intervention period in the experimental group.

6.1.1 Recruitment and retention

The flow of participants into this study is presented in Figure 6.1. During the recruitment period, there were 180 people under the care of the CF centre at Sir Charles Gairdner Hospital (SCGH). Forty-one (23%) were ineligible to participate as they either lived outside the Perth metropolitan area (n = 40) or were unable to read and understand English (n = 1). Of the remaining participants (n = 139), 124 declined to participate. Reasons cited for non-participation included: not willing to travel to SCGH or Osborne Park Hospital for testing or intervention sessions (n = 59); ongoing medical issues limiting participation, including respiratory exacerbation (n = 29); already exercising at least twice per week (n = 14); and being time-poor or 'too busy', or having a work schedule that did not permit participation in the study (n = 7). Four potential participants declined, but did not give a specific reason. A further nine potential participants expressed interest in the study and were provided with a participant information and consent form, but did not respond to phone messages, SMS and/or emails following the clinic visit to further discuss participation in the study. Two potential participants who were colonised with nontuberculous mycobacteria expressed interest in the study, but were not permitted to take part due to the risk of cross-infection in the exercise laboratory. There were 13 adolescents with CF who were screened at Perth Children's Hospital (PCH) and potentially eligible to take part in the study. However, none expressed interest after being provided with the participant information and consent form.

In total, 15 participants were eligible and willing to take part in the study. Prior to undertaking the second baseline assessment session, one participant decided to withdraw from the study and pursue an independent exercise program with a family member. Data collected during the first assessment session on this participant were excluded from any further analysis. The remaining 14 participants were randomised to the experimental (n = 7) or control (n = 7) groups.

Of the seven participants who were allocated to the experimental group, one was unable to complete the intervention due to a motor vehicle accident resulting in multiple fractures and the need for orthopaedic surgery. Scheduled HIIT sessions were undertaken by the participant prior to the accident (n = 4 sessions, the first 2 weeks of the program). Although he was unable to adhere to the HIIT or undertake the follow-up exercise tests, questionnaire data were collected from this participant after a period of 8 weeks (i.e. the designated intervention period of the study) for inclusion in the intention to treat analysis. Of the remaining six participants allocated to the experimental group, five attended at least 80% (i.e. 17 of 22) of the HIIT sessions. One other participant in the experimental group was unable to attend the first follow-up appointment due to other work commitments and therefore he did not contribute data on peak exercise capacity. All other follow-up measures were collected for this participant.

Four participants from the control group reported increases to their regular amount of contact with the CF team during the intervention period. Three of these contacts were related to worsening in respiratory symptoms, and one involved an appointment with a social worker (unrelated to the study). Two participants reported short-term increases in their usual level of exercise participation over the course of the intervention period. One of these instances was due to a participant walking more often in the week as they did not have a car. Another participant reported undertaking more cycling at their gym for a 2-week period, before returning to their baseline level of exercise participation. Four participants in the control group reported symptoms indicative of a respiratory exacerbation. Of these reports, two occurred in week 2, one occurred in week 7 and one occurred in week 8 of the intervention period. These participants were all referred to the CF multidisciplinary team for review via an email or phone call. Following review, all were commenced on oral antibiotics. Two of the four participants completed a course of oral antibiotics and recovered to baseline respiratory function, while the remaining two participants progressed to intravenous antibiotics (one as an inpatient and one as an outpatient). Two participants in the control group were unable to safely undertake the follow-up exercise tests due to being medically unwell for an extended period (requiring oral and intravenous antibiotics).

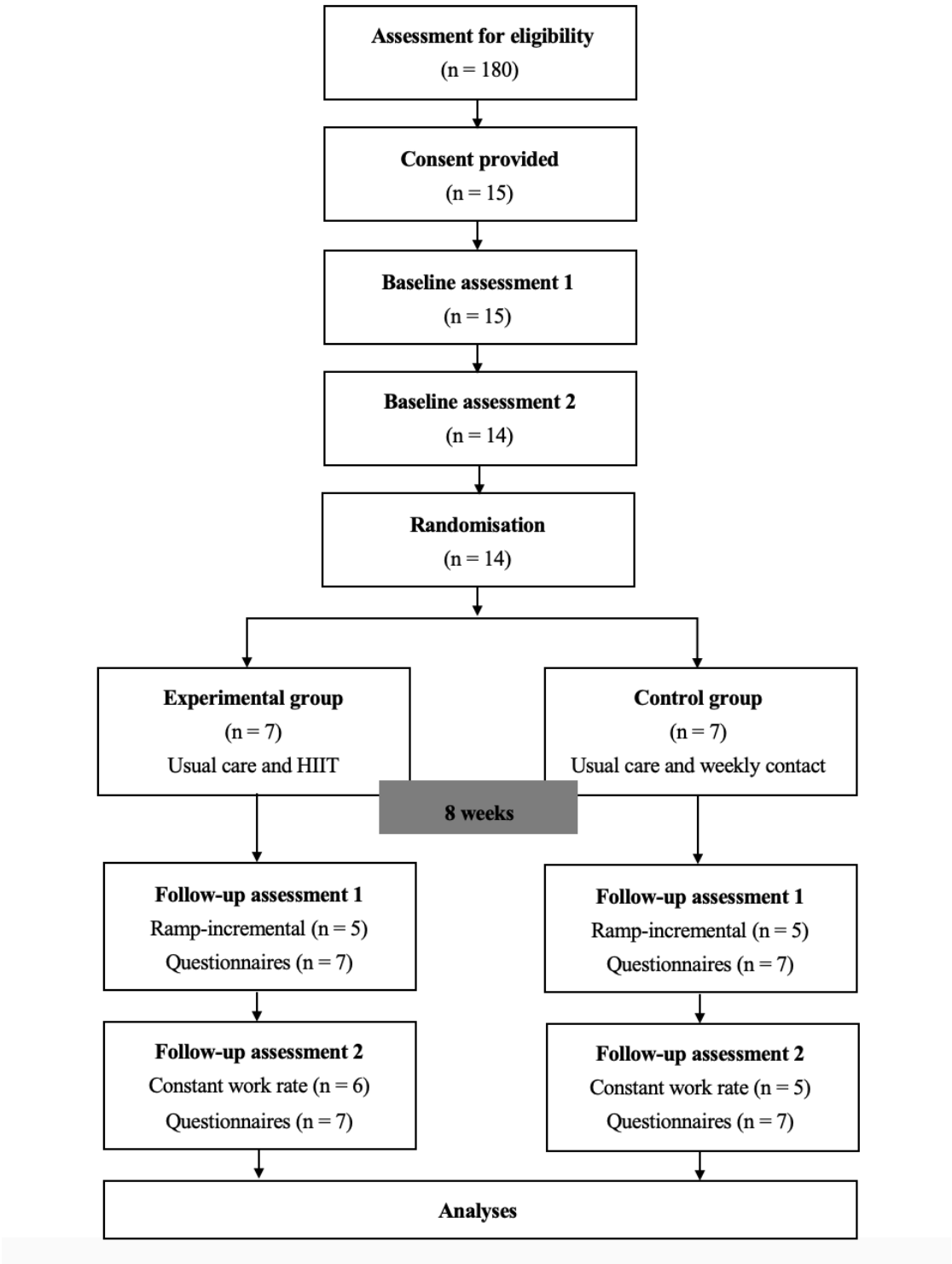


Figure 6.1 Study flow diagram

Notes: During the first baseline and follow-up assessments, the maximal incremental ramp-based cycle ergometry test was performed. During the second baseline and follow-up assessment, the constant work rate cycle ergometry test was performed. Questionnaires were completed across all assessment sessions. The baseline and follow-up assessments were conducted on non-consecutive weekdays across a 2-week period. Reasons for exclusion

following assessment for eligibility and reasons for being unable to undertake the intervention or follow-up assessments are provided in Section 6.1.1.

Abbreviation: HIIT: high intensity interval training.

6.1.2 Participant characteristics

Table 6.1 presents data pertaining to demography and anthropometry, respiratory function and comorbidities. Further data pertaining to the respiratory function of the participants are available in Appendix 5.

Table 6.1 Participant characteristics

Variable	Total sample (n = 14)		Experimental group (n = 7)	Control group (n = 7)
Age (yr)	31 [28, 35]		31 [29, 31]	31 [26, 39]
Height (cm)	176 [163, 182]		172 [163, 183]	179 [159, 182]
Sex (n female [%])	6 [43]		4 [57]	2 [29]
Weight (kg)	75 [64, 92]		75 [64, 101]	76 [63, 92]
BMI ($kg \cdot m^{-2}$)	23.92 [21.40, 30.25]		23.23 [21.40, 34.47]	24.60 [20.53, 28.49]
FEV_1 (L)	2.20 [1.74, 3.40]		2.21 [1.90, 3.40]	1.81 [1.71, 3.58]
FEV_1 (% predicted)	61 [45, 80]		66 [45, 83]	57 [39, 80]
FVC (L)	3.35 [3.07, 5.17]		3.30 [3.00, 5.60]	3.57 [3.07, 5.17]
FVC (% predicted)	82 [64, 95]		88 [62, 100]	79 [64, 92]
FEV_1/FVC (%)	66 [58, 72]		67 [61, 72]	60 [54, 69]
Comorbidity	**n**	**%**		
Asthma	2	14		
CFRD	4	29		
CF-related liver disease	2	14		
Cholelithiasis	2	14		
Ileus	1	7		
OSA	1	7		
Osteopenia	3	21		
Pancreatic insufficiency	10	71		
Reflux	4	29		

Data are presented as median [IQR] unless otherwise stated. Abbreviations: BMI: body mass index, CF: cystic fibrosis, CFRD: cystic fibrosis–related diabetes, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, IQR: interquartile range, OSA: obstructive sleep apnoea. Global Lung Index Initiative lung function reference values used [386].

6.2 Measurements related to the primary research questions

6.2.1 Exercise capacity

Results for the ramp-based cycle ergometry tests are available in Table 6.2. Results for the constant work rate cycle ergometry tests are available in Table 6.3. Individual participant data on peak rate of oxygen uptake (VO_{2peak}) collected during the ramp-based cycle ergometry test and for time to symptom limitation (T_{lim}) during the constant work rate cycle ergometry test measured at baseline and follow-up are illustrated in Figure 6.2 and Figure 6.3, respectively.

6.2.1.1 Ramp-based cycle ergometry test

At baseline, the only measure recorded during the ramp-based cycle ergometry test that differed by a clinically important amount between the experimental and control groups was VO_{2peak} as a percentage of the predicted value (% predicted), which was (median [interquartile range]) 93% [75, 105] in the experimental group and 64% [62, 69] in the control group.

Between-group differences

Compared with the magnitude of change in peak work rate (W_{peak}) (Watts; W) seen in the control group, greater change (increase) in W_{peak} was seen in the experimental group (between-group difference p = 0.017). This increase was also demonstrated when W_{peak} was expressed as % predicted. There were no other between-group differences (Table 6.2).

Within-group differences

In the experimental group, compared with baseline measures, there was a trend for an improvement in the median values of W_{peak} of 11 W (95% confidence interval [CI] 0 to 30). This median difference was equivalent to 6% (95% CI 0 to 10) of the W_{peak} expressed as % predicted. In the experimental group, there was a trend for a median improvement in aerobic threshold represented as a percentage of the VO_{2peak} of 4% (95% CI 0 to 14). No other within-group change was demonstrated in the experimental or control group.

Table 6.2 Baseline and follow-up measures and comparison of between-group change in maximal exercise capacity (end-test measures)

Variable	Experimental group (n = 5)		Control group (n = 5)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
VO_{2peak} ($L \cdot min^{-1}$)	2.25 [1.70, 2.79]	2.76 [2.12, 3.72]	2.25 [1.62, 2.31]	2.25 [1.53, 2.31]	p = 0.50
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	32.57 [22.60, 39.75]	40.75 [28.17, 42.96]	27.14 [21.70, 31.00]	27.14 [20.18, 30.23]	p = 0.20
VO_{2peak} (% predicted)	93 [75, 105]	90 [75, 114]	64 [62, 69]	64 [58, 69]	p = 0.16
VCO_{2peak} ($L \cdot min^{-1}$)	2.84 [2.13, 3.52]	3.20 [2.50, 4.42]	2.74 [2.23, 2.81]	2.20 [2.12, 2.62]	p = 0.27
W_{peak} (Watts)	179 [122, 241]	250 [135, 253]	200 [161, 207]	202 [146, 203]	p = 0.017**
W_{peak} (% predicted)	90 [84, 138]	93 [90, 148]	82 [70, 85]	80 [68, 82]	p = 0.017**
V_{Epeak} ($L \cdot min^{-1}$)	85.44 [60.58, 107.00]	99.50 [74.94, 134.00]	61.37 [60.00, 71.10]	60.66 [56.73, 67.00]	p = 0.10
End-test breathlessness	7 [6, 8]	8 [7, 9]	5 [4, 8]	5 [4, 6]	p = 0.62
End-test leg muscle fatigue	9 [8, 9]	9 [7, 10]	9 [9, 9]	5 [5, 9]	p = 0.25
Nadir SpO_2 (%)	93 [92, 94]	93 [91, 95]	93 [93, 94]	93 [89, 96]	p = 0.71
HR_{max} (bpm)	166 [152, 172]	172 [158, 173]	161 [159, 162]	159 [159, 159]	p = 0.17
HR_{max} (% predicted)	86 [81, 89]	86 [84, 91]	85 [84, 89]	85[83, 88]	p = 0.19
End-test RR ($breaths \cdot min^{-1}$)	44 [40, 51]	44 [42, 50]	32 [31, 43]	33 [30, 40]	p = 0.64
O_2 pulse	14 [11, 16]	16 [11, 21]	14 [11, 15]	14 [11, 15]	p = 0.56
AT (% VO_{2peak})	45 [41, 57]	46 [43, 63]	28 [27, 32]	31 [29, 47]	p = 0.46
VO_2 / work slope ($mL \cdot min^{-1}\ W^{-1}$)	10.40 [9.00, 10.77]	10.39 [9.94, 11.49]	9.70 [9.40, 9.80]	9.72 [8.50, 9.80]	p = 0.58

Ramp-based cycle ergometry test results. Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p values). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: AT: anaerobic threshold, bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, O_2 pulse: oxygen pulse, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, VCO_{2peak}: peak rate of carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake, W_{peak}: peak work rate. End-test symptoms measured using the Borg scale (0 to 10). Predictive values from Jones et al. used for cycle ergometry tests [165, 345].

6.2.1.2 Constant work rate cycle ergometry test

At baseline, the only measure recorded during the constant work rate cycle ergometry test that differed by a clinically important amount between the experimental and control groups was VO_{2peak} % predicted, which was (median [interquartile range]) 92% [67, 105] in the experimental group and 67% [58, 68] in the control group.

Between-group differences

Compared with the magnitude of improvement in T_{lim} (seconds) seen in the control group, greater improvement was seen in the experimental group (between-group difference $p = 0.017$). There were no other between-group differences (Table 6.3).

Within-group differences

In the experimental group, compared with baseline measures, there was an improvement in the median T_{lim} scores of 283 seconds (95% CI 7 to 402; $p = 0.046$). No other within-group change was demonstrated in the experimental or control group.

Table 6.3 Baseline and follow-up measures and comparison of between-group change in endurance exercise capacity (end-test measures)

Variable	Experimental group (n = 6)		Control group (n = 5)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
T_{lim} (s)	276 [222, 360]	555 [317, 620]	248 [238, 262]	230 [228, 262]	p = 0.017**
VO_{2peak} ($L \cdot min^{-1}$)	2.23 [1.60, 2.90]	2.21 [1.69, 2.98]	2.14 [1.43, 2.36]	2.08[1.57, 2.22]	p = 0.27
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	31.48 [21.55, 40.27]	31.8 [22.53, 40.68]	23.47 [20.47, 31.01]	23.47 [19.40, 29.64]	p = 0.27
VO_{2peak} (% predicted)	92 [67, 105]	95 [73, 112]	67 [58, 68]	62 [56, 64]	p = 0.20
VCO_{2peak} ($L \cdot min^{-1}$)	2.46 [1.89, 3.16]	2.39 [1.91, 2.88]	2.60 [2.35, 2.85]	2.29 [2.17, 2.67]	p = 1.00
V_{Epeak} ($L \cdot min^{-1}$)	84.31 [55.91, 104.00]	84.22 [64.00, 107.97]	57.06 [55.61, 68.60]	57.36 [55.79, 67.00]	p = 0.86
End-test Breathlessness	7 [5, 7]	7 [5, 9]	7 [7, 7]	7 [6, 7]	p = 0.36
End-test Leg muscle fatigue	9 [7, 9]	8 [5, 10]	7 [5, 9]	5 [4, 9]	p = 0.92
Nadir SpO_2 (%)	93 [90, 95]	94 [89, 95]	96 [95, 97]	95 [94, 96]	p = 0.13
HR_{max} (bpm)	163 [148, 169]	164 [158, 168]	156 [155, 162]	156 [155, 160]	p = 0.26
End-test RR ($breaths \cdot min^{-1}$)	44 [43, 44]	46 [45, 47]	30 [28, 32]	38 [33, 40]	p = 0.07

Constant work rate cycle ergometry test results. Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p values). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, T_{lim}: time to symptom limitation, VCO_{2peak}: peak rate of carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake. End-test symptoms measured using the Borg scale (0 to 10).

6.2.1.3 Isotime

Between-group differences

Compared with the magnitude of change in end-test VO_2 (% predicted) and heart rate (HR; bpm) seen in the control group, greater change (reduction) was seen in the experimental group (between-group difference p = 0.035 and p = 0.042, respectively) (Table 6.4). There were no other between-group differences.

Within-group differences

Three participants only (all from the control group) achieved a shorter exercise time in the follow-up assessment. In the experimental group, compared with baseline measures, there was a reduction in leg muscle fatigue (Borg score median difference −3, 95% CI −5 to 0), HR (−5 bpm, 95% CI −10 to 0) and minute ventilation (V_E) (−11.74 $L \cdot min^{-1}$, 95% CI −14.93 to −4.30). No other within-group change was demonstrated in the experimental or control group.

Table 6.4 Baseline and follow-up measures and comparison of between-group change in measures collected at isotime during the constant work rate test

Variable	Experimental group (n = 6)		Control group (n = 5)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
T_{lim} (s)	276 [222, 360]	276 [222, 360]	238 [230, 262]	238 [230, 262]	
VO_2 ($L \cdot min^{-1}$)	2.30 [1.59, 2.87]	2.08 [1.55, 2.70]	2.14 [1.43, 2.18]	2.10 [1.58, 2.30]	p = 0.07
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	31.50 [21.55, 40.27]	28.80 [20.71, 40.53]	23.47 [20.45, 29.64]	23.46 [20.5, 30.53]	p = 0.07
VO_2 (% predicted)	92 [67, 105]	87 [63, 107]	62 [58, 64]	64 [56, 68]	p = 0.035**
VCO_2 ($L \cdot min^{-1}$)	2.45 [1.89, 3.16]	2.29 [1.65, 2.91]	2.60 [2.35, 2.67]	2.29 [2.23, 2.75]	p = 0.36
V_E ($L \cdot min^{-1}$)	84.31 [55.91, 104.00]	72.32 [48.30, 89.00]	57.06 [55.61, 67.00]	58.80 [55.79, 70.00]	p = 0.10
Breathlessness	7 [5, 7]	5 [3, 6]	7 [6, 7]	7 [5, 7]	p = 0.93
Leg muscle fatigue	9 [7, 9]	6 [2, 8]	7 [5, 9]	5 [4, 9]	p = 0.09
SpO_2 (%)	96 [93, 97]	95 [90, 95]	95 [94, 98]	96 [95, 96]	p = 0.52
HR (bpm)	163 [148, 169]	156 [138, 166]	156 [155, 160]	156 [155, 156]	p = 0.042**
RR ($breaths \cdot min^{-1}$)	44 [43, 44]	37 [31, 49]	33 [32, 38]	31 [28, 40]	p = 0.14

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (p value). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: bpm: beats per minute, HR: heart rate, IQR: interquartile range, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, T_{lim}: time to symptom limitation, VCO_2: carbon dioxide production, V_E: minute ventilation, VO_2: oxygen uptake. End-test symptoms measured using the Borg scale (0 to 10).

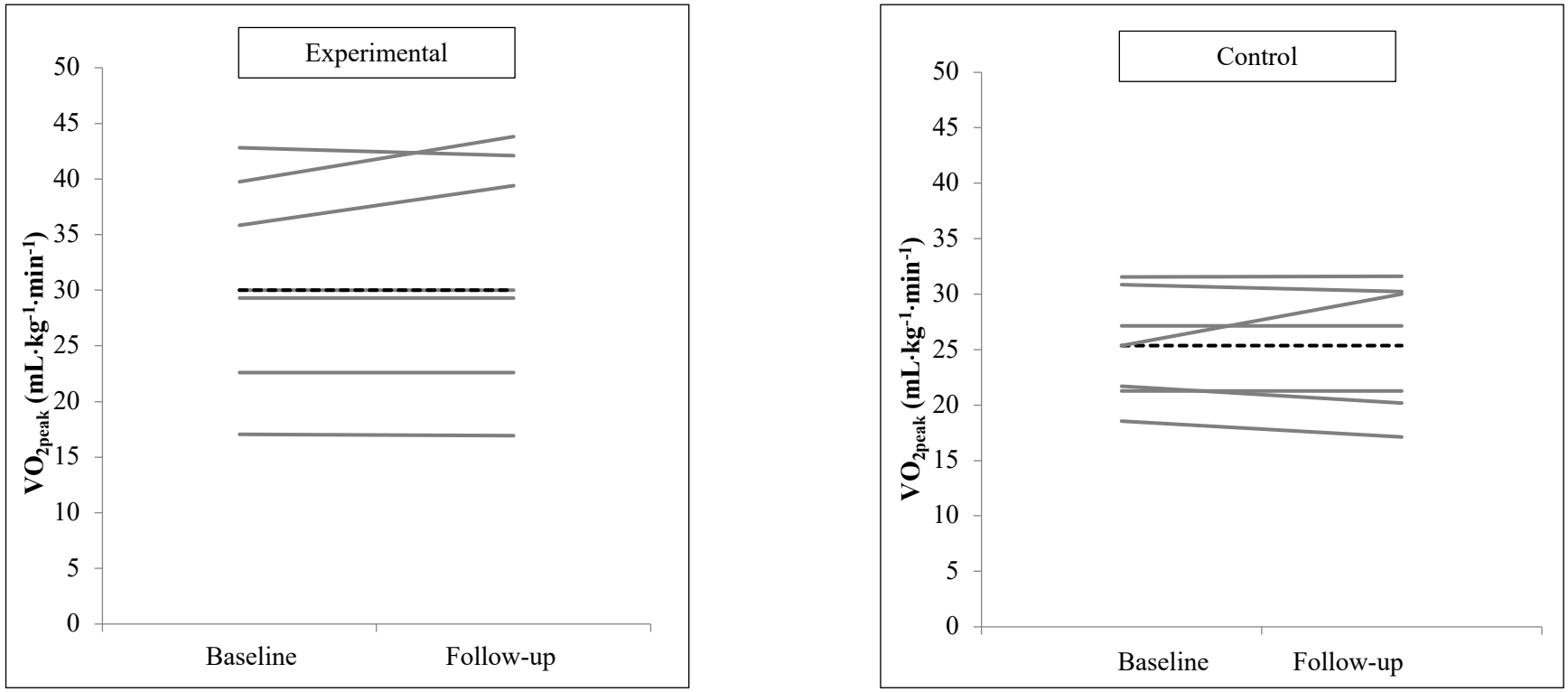


Figure 6.1 Plots of each participant's data for peak rate of oxygen uptake measured at baseline and follow-up during the ramp-based cycle ergometry test

Individual participant responses (—); median response for the group (- - -). Abbreviation: peak rate of oxygen uptake (VO_{2peak}).

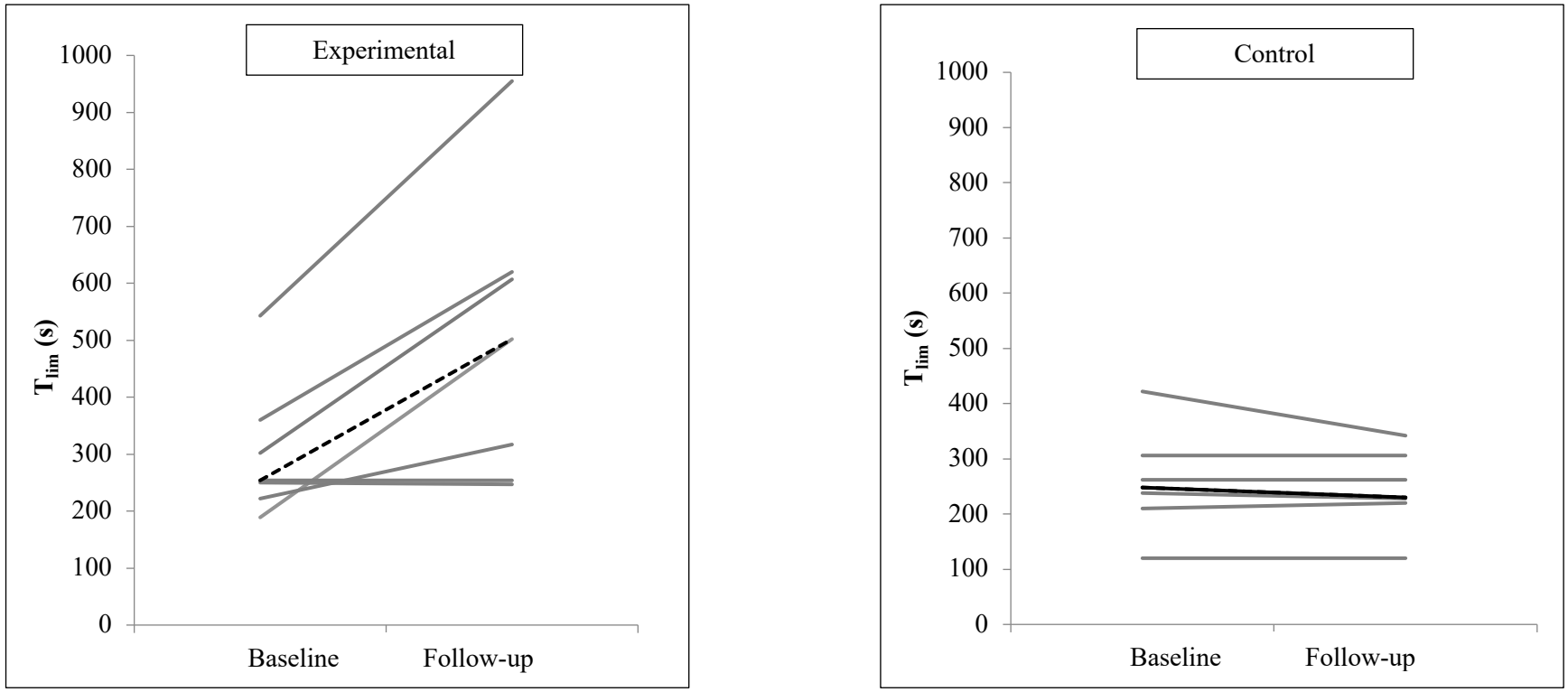


Figure 6.2 Plots of each participant's data for time to symptom limitation measured at baseline and follow-up during the constant work rate cycle ergometry test

Individual participant responses (—); median response for the group (- - -). Abbreviation: time to symptom limitation (T_{lim}).

6.2.1.4 Baseline observation carried forward – exercise capacity

Overall, the results of the original analyses (Section 6.2.1.1–6.2.1.3) and the analysis using the baseline observation carried forward (BOCF) method (presented in Appendix 4) were comparable. The only result that was not comparable was the within-group difference in T_{lim} in the experimental group. Unlike the confidence intervals for the median difference of 283 (95% CI 7 to 402) seconds demonstrated in the original analysis, the 95% CI of the median difference of 260 seconds found in the BOCF crossed zero (95% CI −2 to 381). However, a between-group difference in T_{lim} was still demonstrated using the BOCF ($p = 0.017$).

6.2.2 Health-related quality of life

Between-group analysis of HRQoL measures is presented in Table 6.5. The individual participant plots for HRQoL in experimental and control groups are presented in Figure 6.4. At baseline, the experimental and control groups reported similar HRQoL (Cystic Fibrosis Questionnaire Revised [CFQ-R] and Alfred Wellness Score for CF [AweScore-CF]).

Between-group differences

Compared with the magnitude of improvement in the physical function domain of the CFQ-R seen in the control group, greater change (improvement) was seen in the experimental group (between-group difference $p = 0.03$) (Table 6.5). There were no other between-group differences.

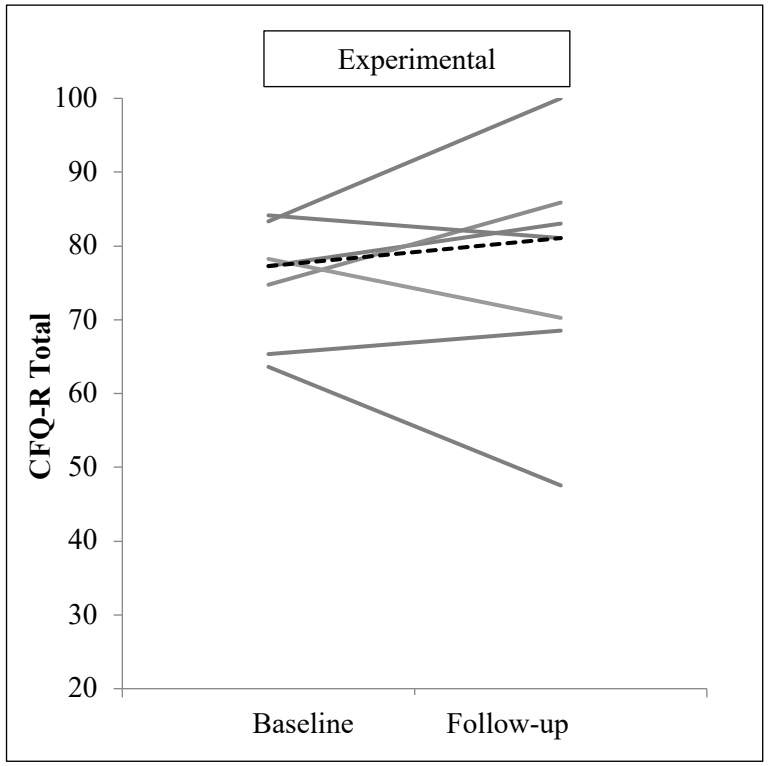
Within-group differences

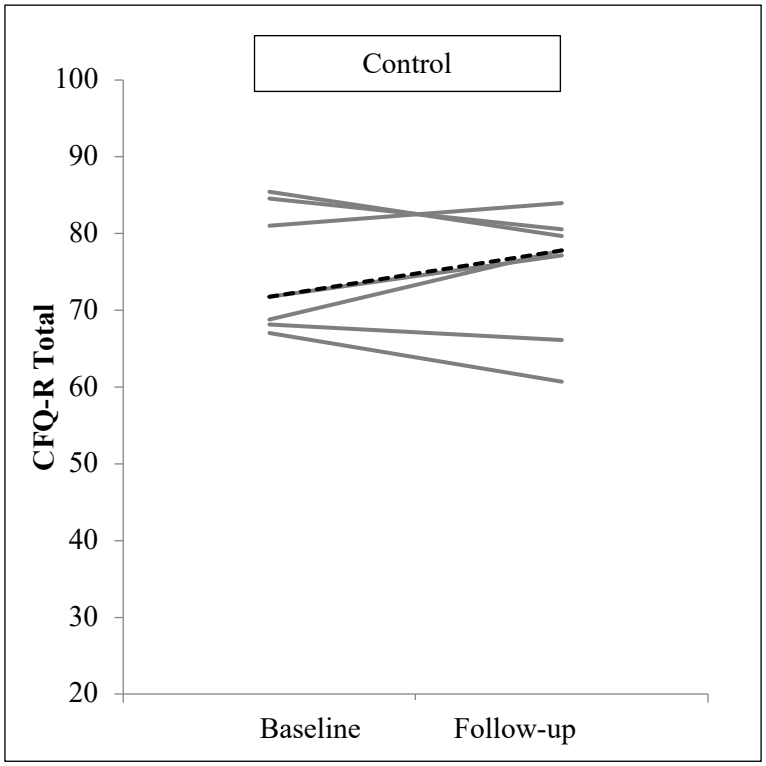
Compared with baseline measures, there were no differences observed in any domain of the CFQ-R or AweScore-CF for the experimental or control group.

Table 6.5 Baseline and follow-up measures and comparison of between-group change in health-related quality of life

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
CFQ-R (total)	72 [65, 83]	81 [69, 86]	72 [68, 85]	78 [66, 81]	p = 0.66
Physical function	75 [54, 92]	88 [63, 100]	92 [50, 92]	79 [50, 96]	p = 0.033**
Vitality	50 [42, 75]	58 [33, 67]	50 [42, 75]	58 [42, 67]	p = 0.95
Emotional function	80 [73, 100]	87 [67, 100]	87 [73, 93]	87 [67, 87]	p = 0.44
Eating disturbance	100 [100, 100]	100 [89, 100]	100 [89, 100]	100 [89, 100]	p = 0.62
Treatment burden	67 [11, 78]	56 [22, 67]	56 [44, 67]	56 [44, 67]	p = 0.95
Health perception	67 [44, 89]	78 [56, 89]	67 [44, 78]	56 [44, 67]	p = 0.14
Social function	72 [61, 83]	72 [56, 83]	72 [67, 78]	72 [67, 83]	p = 0.25
Body image	78 [67, 89]	67 [56, 89]	56 [56, 100]	67 [56, 100]	p = 0.22
Role limitations	92 [67, 100]	92 [83, 100]	83 [75, 92]	83 [75, 92]	p = 0.56
Weight problems	100 [33, 100]	100 [33, 100]	100 [67, 100]	100 [67, 100]	p = 0.79
Respiratory symptoms	72 [50, 72]	72 [44, 89]	72 [56, 89]	67 [56, 83]	p = 0.18
Digestive symptoms	100 [89, 100]	89 [78, 100]	78 [78, 100]	78 [78, 89]	p = 0.30
AweScore-CF (total)	65 [50, 66]	62 [55, 67]	63 [48, 74]	65 [51, 69]	p = 0.85

Data are presented as median [IQR]. Between-group difference data were analysed using rank-sum tests (reported as p value). Greater scores reflect a better outcome for both questionnaires. **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: AweScore-CF: Alfred Wellness Score for Cystic Fibrosis, CFQ-R: Cystic Fibrosis Questionnaire Revised.


Experimental
CFQ-R Total
100
90
80
70
60
50
40
30
20
Baseline
Follow-up


Control
CFQ-R Total
100
90
80
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40
30
20
Baseline
Follow-up

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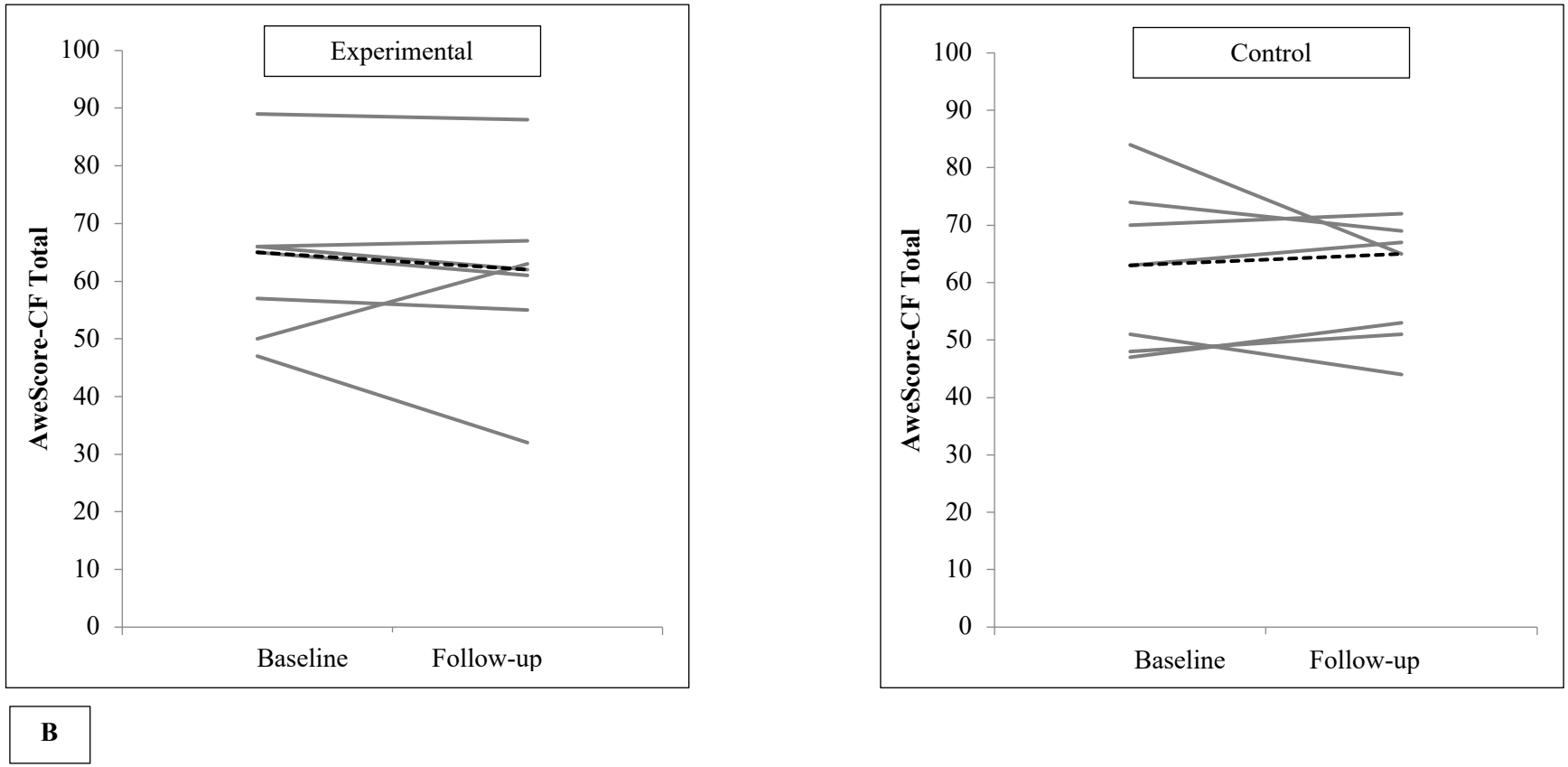

Figure 6.3 Plots of each participant's data for health-related quality of life measured at baseline and follow-up

Individual participant responses (—); median response for the group (- - -). Graph A: Cystic Fibrosis Questionnaire Revised; Graph B: Alfred Wellness Score for Cystic Fibrosis. Greater scores reflect a better outcome for both questionnaires.

6.2.3 Exercise self-efficacy

Between-group analysis of exercise self-efficacy measures is presented in Table 6.6. The individual participant plots for exercise self-efficacy in the experimental and control groups are available Figure 6.4. At baseline, the experimental and control groups reported similar levels of exercise self-efficacy (Barriers Self-Efficacy Scale [BARSE]).

Between-group differences

There were no between-group differences in the magnitude of change for the BARSE following the intervention period (Table 6.6).

Within-group differences

Compared with baseline measures, there were no differences observed in the BARSE for the experimental or control group.

Table 6.6 Baseline and follow-up measures and comparison of between-group change in exercise self-efficacy

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
BARSE (total)	59 [47, 78]	55 [35, 68]	48 [31, 64]	37 [34, 67]	p = 0.90

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p value). Greater scores reflect a better outcome. Abbreviation: BARSE: Barriers Self-Efficacy Scale.

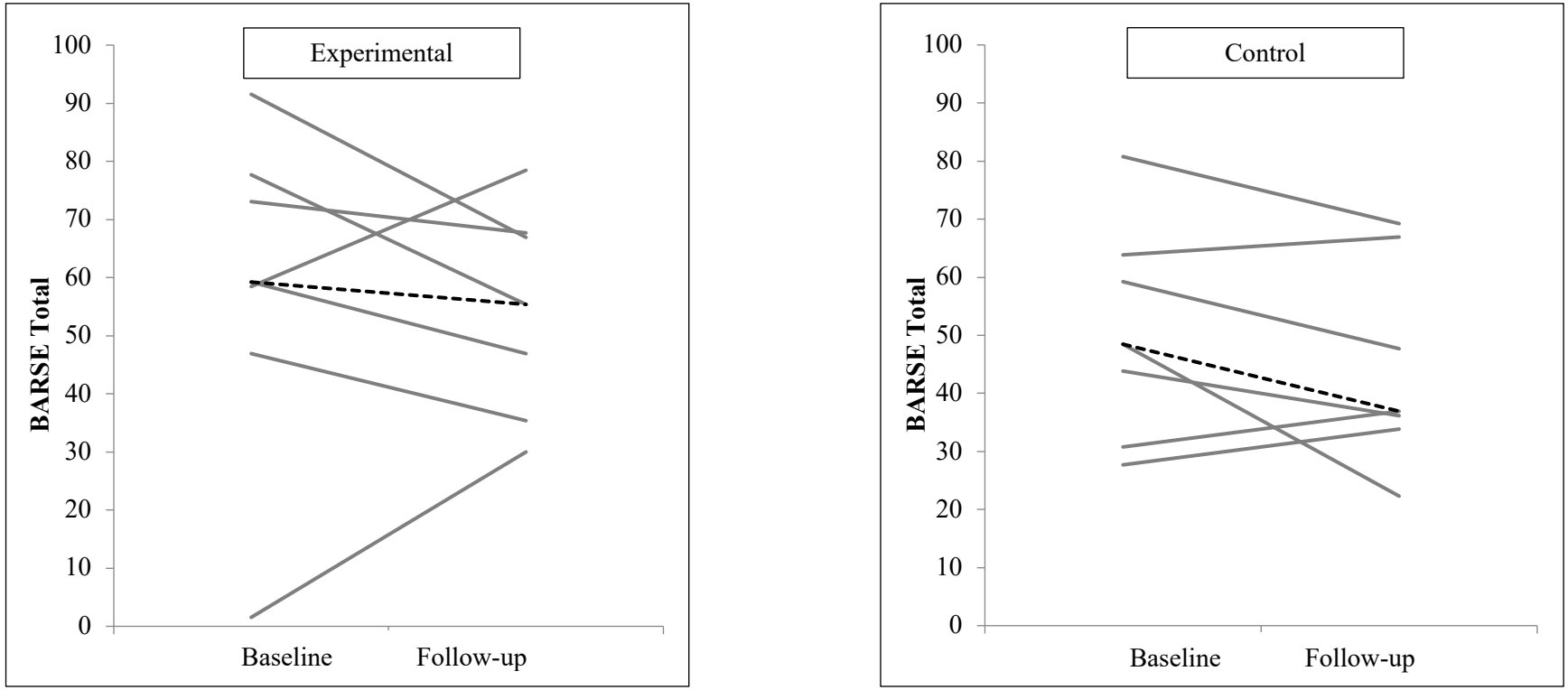

Figure 6.4 Plots of each participant's data for exercise self-efficacy measured at baseline and follow-up

Individual participant responses (—); median response for the group (- - -). Greater scores reflect a better outcome.

Abbreviation: BARSE: Barriers Self-Efficacy Scale.

6.2.4 Feelings of anxiety and depression

Between-group analysis of exercise self-efficacy measures is presented in Table 6.7. The individual participant plots for the Hospital Anxiety and Depression Scale (HADS) for the experimental and control groups are presented in Figure 6.6. At baseline, the experimental group reported higher feelings of depression (HADS total 8) compared to the control group (HADS total 4).

Between-group differences

There were no between-group differences in the magnitude of change for the HADS following the intervention period (Table 6.7).

Within-group differences

Compared with baseline measures, there were no differences observed in the HADS (total or when separated into the anxiety and depression domains) for the experimental or control group.

Table 6.7 Baseline and follow-up measures and comparison of between-group change in feelings of anxiety and depression

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
HADS (total)	8 [4, 14]	8 [3, 15]	4 [3, 8]	7 [3, 8]	p = 0.95
Anxiety	5 [3, 10]	6 [3, 9]	3 [3, 6]	4 [1, 6]	p = 0.61
Depression	3 [2, 4]	2 [1, 4]	1 [0, 1]	2 [1, 2]	p = 0.32

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p value). Lower scores reflect a better outcome. Abbreviation: HADS: Hospital Anxiety and Depression Scale.

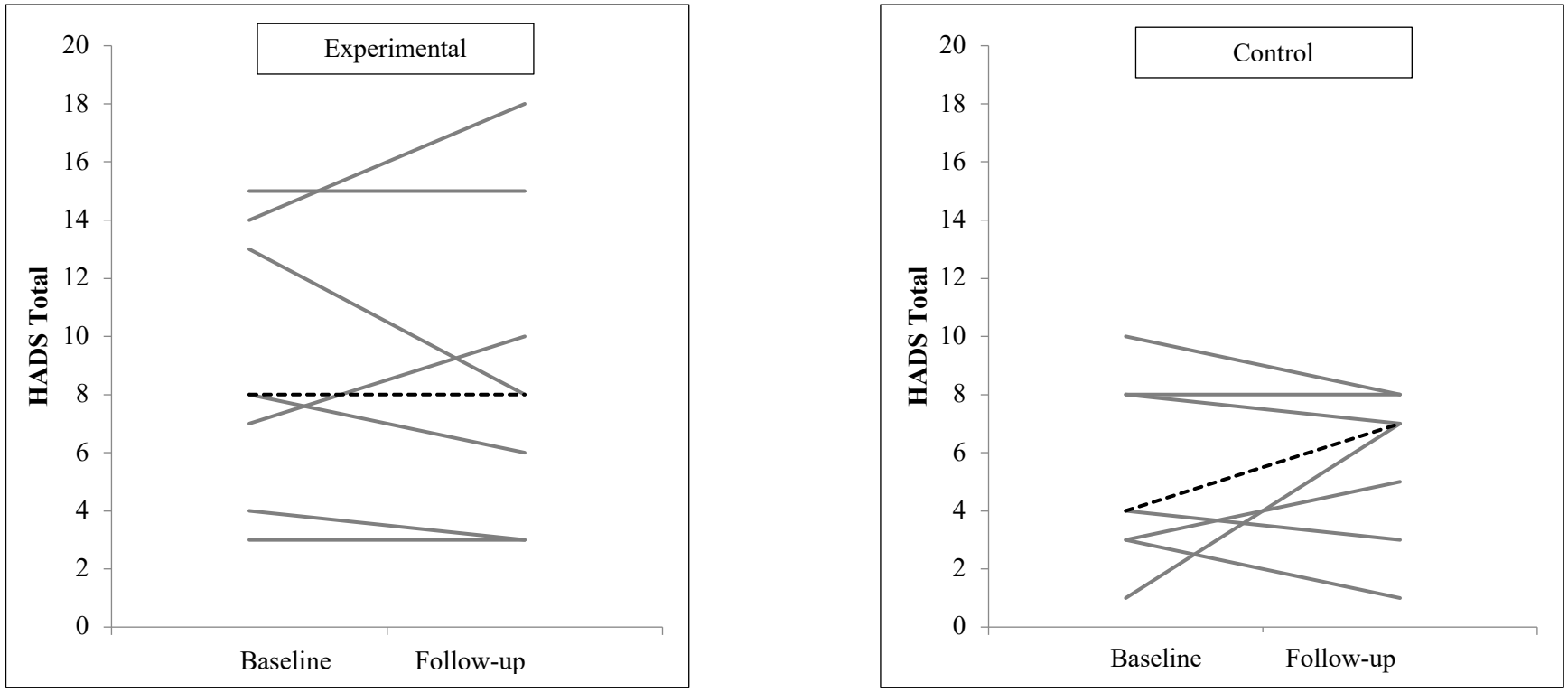

Figure 6.5 Plots of each participant's data for feelings of anxiety and depression measured at baseline and follow-up

Individual participant responses (—); median response for the group (- - -). Lower scores reflect a better outcome.

Abbreviation: HADS: Hospital Anxiety and Depression Scale.

6.2.5 Exercise enjoyment

Between-group analysis of exercise enjoyment measures is presented in Table 6.8. The individual participant plots for the Physical Activity Enjoyment Scale (PACES) in experimental and control groups are given in Figure 6.7. At baseline, the experimental and control groups reported similar enjoyment with exercise.

Between-group differences

There were no between-group differences in the magnitude of change for the PACES following the intervention period (Table 6.8).

Within-group differences

Compared with baseline measures, there were no differences observed in the PACES for the experimental or control group.

Table 6.8 Baseline and follow-up measures and comparison of between-group change in exercise enjoyment

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
PACES (total)	38 [18, 44]	44 [24, 51]	32 [25, 49]	36 [17, 45]	p = 0.12

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p value). Greater scores reflect a better outcome. **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviation: PACES: Physical Activity Enjoyment Scale.

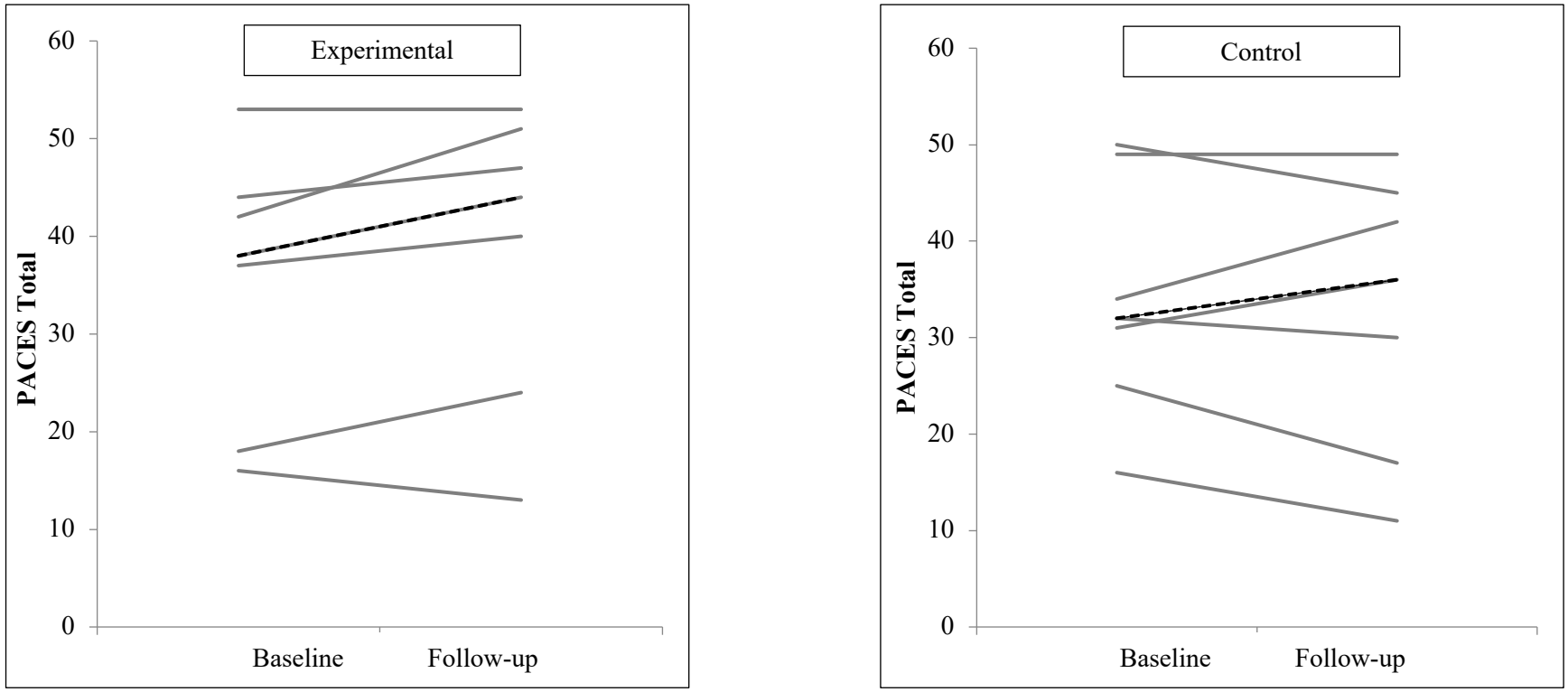

Figure 6.6 Plots of each participant's data for exercise enjoyment measured at baseline and follow-up

Individual participant responses (—); median response for the group (- - -). Greater scores reflect a better outcome.

Abbreviation: PACES: Physical Activity Enjoyment Scale.

6.3 Measurements related to the secondary research questions (experimental group only)

6.3.1 Post-exercise muscle soreness

Four of the seven participants reported post-exercise muscle soreness on a single occasion each over the 8-week intervention period. The severity of these symptoms was mild in all cases (median [IQR] 8 mm [5 to 8] out of 100 mm on a VAS).

6.3.2 Tolerance and exercise intensity

The median [IQR] percentage of sessions attended by participants in the experimental group was 93% [83, 95]. Of the sessions attended, 100% of the participants were able to complete each session in its entirety. Only one participant attended less than 80% (77%) of the designated HIIT sessions. Another participant in the experimental group completed 6 weeks (rather than the designated 8 weeks) of the HIIT due to unforeseen work-related travel obligations. However, of the 6-week intervention period that the participant undertook, an attendance record of 100% was achieved. Reasons provided by participants who missed individual HIIT sessions included work commitments (n = 9), travel (n = 1) and family commitments (n = 2).

Participants allocated to the experimental group were able to achieve a median [IQR] intensity of 111% [83, 132] of their baseline W_{peak} during the final 2 weeks of the intervention period (Figure 6.7). In all participants, SpO_2 did not fall by > 4% of pre-exercise levels throughout the intervention period. There were no minor or major adverse events during the assessment or intervention periods

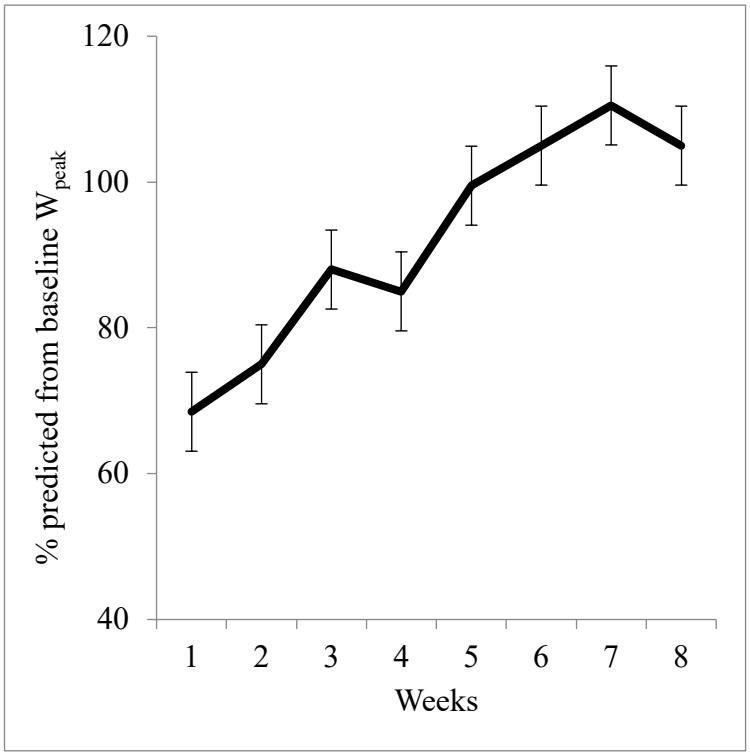

Figure 6.7 Intensity achieved per week during high intensity interval training program

Data are presented as median and interquartile range. Abbreviation: W_{peak}: peak work rate.

6.3.3 Debrief interviews

Of the seven participants allocated to the experimental group, the one participant who completed four HIIT sessions was not invited to undertake a debrief interview. Of the remaining six participants, five agreed to undertake a debrief interview and one did not respond to three contact attempts from the PhD candidate to arrange an interview session. Of the five participants who undertook the debrief, two interviews were conducted in conjunction with routine clinical appointments at SCGH, and the other three interviews took place outside of clinic appointments.

6.3.3.1 Facilitators to participation in the HIIT program

Four major themes surrounding facilitators to participating in the HIIT program were identified during the debrief interviews. These themes were: (i) tolerability, (ii) commitment and flexibility, (iii) enjoyment, and (iv) the presence of a therapist during the HIIT sessions. The themes and corresponding phrases to support each theme (verbatim) from the debrief interviews are presented in Table 6.9.

Table 6.9 Debrief themes – facilitators

Tolerability	"The first couple times my legs were a bit sore, but it wasn't really that much, it wasn't unbearable, it wasn't like it hurt to walk or anything like that" [P2] "I actually felt more energised afterwards" [P2] "It was certainly challenging, it wasn't a walk in the park, but then the feeling I got after I had done a session was like an adrenaline rush… it was really motivating" [P8] "Most of the time it was my legs that got to me more than my breathing" [P8] "If I was having a bad day with my lungs, that was more effort [to attend], but I also know that when I felt that way we just adjusted the intensity that day accordingly, so I didn't ever feel like I was going to 'over-do' it" [P8] "I was never sore, I never had leg pain or anything like that… I always felt good after, more energy and motivation" [P9] "I never had muscle soreness or anything like that, I knew I had done exercise, but that was it" [P11] "It wasn't so hard that I couldn't do it, but hard enough that it pushed me" [P14]
Commitment / Flexibility	"It was easy to do because it was only 10 minutes, you only had to sweat it out for 10 minutes" [P2] "It was quite flexible with my work schedule" [P2] "The sessions weren't 'easy' but the fact that it was a small amount of time really worked for my schedule" [P2] "It didn't have a massive impact on my routine" [P8] "If I did a good session, I didn't feel like I needed much else [additional exercise]" [P8] "The fact that the physio was so available [to supervise] all the time, to fit in with my schedule. I liked that" [P9] "The fact that it was quick and it was going to be over soon, it's like, I can do this" [P9]

Enjoyment	"The actual sessions were challenging, but as much as they were challenging, I felt a real adrenaline rush after them, and it felt like a sense of achievement after each session, so yeah, really positive, I enjoyed it" [P8] "My experience overall was really positive, this was higher intensity exercise and a different style to how I would normally exercise. I really enjoyed that" [P8] "I was buzzing after doing the study, I even tried some interval running after the study finished with some friends" [P8] "I got into a routine, coming in here, I enjoyed it… it was an enjoyable experience" [P11] "You look forward it" [P9] "Short and sweet… I really enjoyed it!" [P9] "I really enjoyed it… I am sad that it is finishing, I probably will incorporate it into my routine going forward" [P11] "I would test myself, using the Watts on the bike, I could see the number, so I actually really enjoyed that, I would definitely incorporate it [the training] into my daily, weekly exercise routine, yeah, I enjoyed it" [P11] "I really enjoyed the structure of it [the program], having to be at a certain place at a certain time, it gave me focus" [P14] "I think because I enjoyed it, that was a real enabler [for me to continue]" [P14]
Therapist presence	"Having the little cheer squad on the side really helps, because it is not something that I would probably do on my own. I think having the physio there to go 'ok let's get this done' is much easier" [P2] "The supervision component was definitely motivating, I liked the structure" [P8] "The supervision component was really beneficial" [P8] "Having someone here, and knowing you're only going to be exercising for a little bit makes it better" [P9] "I like to be pushed" [P9] "Having the intensity [Watts] and the number of bars [intervals] remaining on the screen, we also spoke about the heart rate; I liked having information and feedback because it helped me motivate and challenge myself for the next session, so yeah, I felt like I had good information from the physiotherapist throughout" [P11] "Knowing there was going to be someone supervising, you couldn't just miss a session because you'd be letting someone down. I think I enjoyed that, it was a real enabler" [P11] "Say, for example I had the equipment at home or at the local gym, and you said 'go three times per week', I probably wouldn't have felt as motivated, but having someone to encourage along the way, it is something different to what I have had before" [P14]

Note: P = participant number.

6.3.3.2 Barriers to participation in the HIIT program

In addition to the perceived facilitators to participating in the HIIT program, a number of actual and/or potential barriers to participating were identified during the interviews. These barriers fell into the following themes: (i) perceived or actual lack of internal motivation to undertake exercise, (ii) the travel time associated with session visits, (iii) life commitments, and (iv) the impact of the disease process. Examples from the interview transcripts (verbatim) are listed in Table 6.10.

Table 6.10 Debrief themes – barriers

Internal motivation	"If I skipped one session, it was tougher the next time" [P2] "Motivation for me is a tough one, like I said, I didn't like, I still don't like exercise, and it is not something I will ever be comfortable with, yep, not my thing… that was probably my biggest struggle, the motivation to do it, and I found if I missed a session, it was even harder the next time" [P2] "I reverted back to my old ways after finishing the program, but I don't have the equipment [bike] at home, so I wasn't going to continue anyway…" [P2] "I am not one for exercise… I kind of feel like I am allergic to it!" [P2] "I don't know what to do if I am by myself, what [exercise] is going to be effective and what's not" [P9] "I think if I am going to do it [the HIIT] on my own, I need to find the right gym… because I need the motivation" [P9] "Probably just not having the motivation [is the main barrier to exercise]. When someone is there with a plan… it is probably just my own laziness when it comes down to it, I need to stop being lazy" [P9] "I haven't done any exercise since [completing the program]" [P9] "Once you make a commitment to someone, you can't change it, so it was like 'I have to go' [to the HIIT sessions], whereas now I will be on my own, it could be easier to tell myself I don't feel like it today" [P11] "If I hadn't enjoyed the sessions, that would have been a barrier" [P11] "Some days I just don't have the energy [to exercise]… it's the motivation, definitely" [P14]
Travel / location	"The main thing was finding parking" [P2] "Being at home would be better" [P2] "I was lucky that I worked down the road, so if it was any further, that would have been a barrier" [P8] "I don't have any [barriers]. It's easy for me… I live close and parking wasn't an issue" [P11] "I work close by and live close by, so it was easy. Whereas if I perhaps lived or worked further away, it might have been more effort to get there" [P14]
Life / other commitments	"Having CF I am pretty busy, and I've got a child, and a full-time job, I work long hours, so it is important to me for it [exercise] to be flexible" [P2] "Mainly just work [was a barrier]… having to go around work" [P9] "If the sessions were longer, that could have been a barrier… trying to fit it in with everything else" [P14]
Disease	"It was tough during the time when I wasn't well, but I was still able to do it [the HIIT]" [P2] "If I was having a bad day with my lungs, that was more effort [to attend], but I also know that when I felt that way we just adjusted the intensity that day accordingly, so I didn't ever feel like I was going to 'over-do' it" [P8] "I guess if you are feeling sick it is obviously harder to exercise" [P9] "The better I am feeling, the more likely I am to go [to exercise]" [P14] "When you feel unwell, and then you have all your medication and you have to try and schedule exercise in, it's just hard" [P14]

6.4 Discussion

This is the first RCT to evaluate the effects of 8 weeks of low-volume HIIT on exercise capacity, HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. This RCT demonstrated that 8 weeks of low-volume HIIT produced greater magnitude of change in T_{lim} and W_{peak} over and above the magnitude of change by continuing usual care (control group) in people with CF. Improvements in T_{lim} and W_{peak} were demonstrated despite the time commitment of the HIIT program being only 30 minutes per week. There were no changes in any other parameters of aerobic fitness. However, W_{peak} has shown similar prognostic utility for survival and/or need for lung transplantation at 10-year follow-up to other measures such as VO_{2peak} in people with CF [38]. The HIIT program was well tolerated and accepted by participants of the experimental group. Compared to participants allocated to the control group, those in the experimental group also reported increased physical functioning as measured by the CFQ-R. There were uncertain between-group effects for the other outcomes.

The control group maintained stable exercise capacity throughout the 8-week intervention period. Stability in these measures in the control group, particularly the stability of T_{lim} and W_{peak}, increases our confidence in attributing the between-group difference to the HIIT program. Further, there was a trend towards a reduction in HR, V_E, VCO_2 and leg fatigue at isotime in the experimental group, which provides evidence that the HIIT program induced a physiological training adaptation associated with conditioning of skeletal muscles (i.e. the quadriceps) and the cardiovascular system. This is supported by data in healthy young adults (n = 8, mean ± standard deviation, aged 22 ± 1 years, VO_{2peak} 45 ± 3 $mL \cdot kg^{-1} \cdot min^{-1}$) which demonstrated that as few as six sessions of cycling-based HIIT over 2 weeks elicited a physiological training response by producing improvements in the peripheral skeletal muscles (i.e. vastus lateralis) that are indicative of increased oxidative capacity, for example, an increase of 38% in citrate synthase levels from the baseline level [285]. In another study of healthy but sedentary men, after 12 weeks of HIIT (n = 9), moderate intensity continuous exercise (n = 10) or no exercise (n = 6), between-group differences in citrate synthase levels were demonstrated in the exercise groups ($p < 0.001$; unable to determine confidence intervals from data provided), in particular the HIIT group, compared to the control group. This was despite the time commitment and exercise volume of the HIIT program being fivefold lower than the moderate intensity continuous exercise (10 minutes compared to 50 minutes per session) [286].

The results of this RCT build on the limited data available regarding the effect of the HIIT approach in people with CF [34, 60, 302, 303]. Specifically, one previous randomised trial, available only as a conference abstract, implemented a HIIT protocol in this clinical population (n = 24, age and forced expiratory volume in 1 second [FEV_1] not reported) [60]. The intervention involved 30 seconds of cycling at 100% of the W_{peak} interspersed with 30 seconds of cycling at 40% of the W_{peak} for a duration of 30 minutes per session. This intervention was matched for workload with a moderate intensity continuous exercise training program, with the two modes of exercise training found to have a comparable effect on exercise capacity (mean difference [MD] 1 W, 95% CI −51 to 49). A training effect was also seen in 6-minute walk distance (6MWD) (MD 19 m, 95% CI −41 to 79). Considering the wide CIs for both W_{peak} and 6MWD, this study was unable to demonstrate equivalence of the two training protocols given the true effect could span between −51 and 49 m. As such, this study was likely not powered to demonstrate a between-group effect in these outcomes. Another study compared a HIIT program to a 'standard' exercise program in people with CF who had severe respiratory disease (n = 23) [34]. Where possible, participants (aged 26 ± 10 years, FEV_1 32 ± 4% predicted) completed a continuous training program on a treadmill (45 minutes of exercise at 60 to 70% VO_{2peak}). Participants were only allocated to the HIIT group (aged 26 ± 8 years, FEV_1 26 ± 8% predicted) if they were unable to tolerate continuous training. The HIIT program comprised 30 seconds of walking at the individual's comfortable continuous walking speed (between 3 and 4 km/h) at 50% of the grade achieved during a steep-ramp test on a treadmill (modified Balke-protocol), interspersed with 60 seconds of 'rest' (walking at 0% treadmill inclination). This work to rest cycle was repeated 10 times. On completion of the training program, both groups improved their VO_{2peak} (−1 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI −5 to 3]). Participants in the HIIT group reported the program to be 'motivating and less strenuous' than their previous experience with moderate intensity continuous exercise. These results must be interpreted with caution because, in this study, group allocation was not decided through a process of randomisation [34]. The present RCT is the first to show that as little as 30 minutes of HIIT per week for 8 weeks can substantially increase exercise capacity, compared to no formal exercise training, in people with CF.

The maximal incremental cardiopulmonary exercise test (CPET) was chosen to assess peak exercise capacity as it is the 'gold-standard' measurement tool to assess exercise capacity in people with CF [39, 161]. The constant work rate cycle ergometry test was chosen as the primary measurement tool (with T_{lim} being the primary outcome) due to its responsiveness to detect changes in the effectiveness of interventions [42]. Without measuring each participant's critical power (i.e. the intensity that can be sustained indefinitely), it can be

difficult to select an appropriate work rate for the constant work rate cycle ergometry test. The work rate needs to be above the critical power, but also produce a baseline T_{lim} that is likely to be responsive. Given the hyperbolic relationship between power and duration [351], tests that are done well above the critical power will produce a short T_{lim}, which compromises their responsiveness. Likewise, tests that are done too close to the critical power will produce a long T_{lim}, and their responsiveness is likely to be compromised by a ceiling effect (i.e. the investigator ceasing the test after a fixed time, e.g. 20 minutes). In other populations with chronic lung disease, the work rate chosen for constant work rate cycle ergometry tests is usually between 75 and 80% of the W_{peak} achieved during a ramp-based cycle ergometry test [42]. For this study, 80% of the W_{peak} was chosen. It is acknowledged that alternative laboratory-based submaximal exercise testing protocols, such as the steep ramp test, are available in people with CF. However, the constant work rate cycle ergometry test at 80% of the $W_{peak\ with}$ breath-by-breath analysis has been demonstrated to be: (i) feasible; (ii) responsive [325]; and (iii) highly repeatable, having a within-subject coefficient of variation of 6% [170].

The primary outcome of exercise capacity (T_{lim}), which was set *a priori*, improved by 100% following the intervention period in the experimental group. Consistent with data in people with chronic obstructive pulmonary disease (COPD), the current study has demonstrated that T_{lim}, which is traditionally used as a measure of submaximal endurance exercise capacity, is highly responsive in people with CF, and more responsive than measures obtained during a ramp-based cycle ergometry test. Although the use of the constant work rate cycle ergometry tests is novel in people with CF, results are likely to be more meaningful to clinicians and patients, because activities of daily living are usually undertaken at a submaximal exercise intensity, rather than peak exercise capacity. To this effect, clinicians could explain to patients that improving T_{lim} would translate to an improvement in their ability to perform daily activities for longer. The minimal clinically important difference (MCID) for T_{lim} in people with CF is yet to be established. However, in other chronic cardiorespiratory conditions, such as COPD, the MCID is estimated at 100 seconds [42]. In the current RCT, all participants allocated to the experimental group who completed both the baseline and follow-up constant work rate cycle ergometry test demonstrated an improvement greater than 100 seconds from baseline to follow-up, which may be a clinically meaningful improvement in exercise endurance capacity in people with CF.

Compared to the control group, there was no clear effect on the gold-standard measure of exercise capacity (VO_{2peak}) in the experimental group at the end of exercise training. This was unexpected, as HIIT in healthy people and other chronic respiratory populations has

produced improvements in VO_{2peak} [286]. The reason for this lack of response in VO_{2peak} as well as other indices of aerobic fitness that may have prognostic relevance is likely to be multi-factorial. The first explanation may be related to the initial fitness level of the participants. That is, participants allocated to the experimental group had a higher VO_{2peak} at baseline compared to the control group. We speculate that improvements in VO_{2peak} may be more modest in people with CF who have a higher level of baseline VO_{2peak}. This notion has been contended previously, but not thoroughly investigated in other chronic respiratory populations [352]. Another explanation may be related to the timeframe of the intervention period. Eight weeks is commonly used in standardised exercise programs such as pulmonary rehabilitation and was decided upon based on the available timeframe for this program of research. However, a systematic review (Chapter 7, Part 1) demonstrated that longer exercise training interventions are likely to be more advantageous than shorter interventions at optimising participation in exercise training in young people with chronic cardiorespiratory conditions [270]. Indeed, 3 to 6 months of training may have resulted in meaningful gains in VO_{2peak}. Finally, the small sample size of this RCT is likely to reduce the ability to detect a between-group change in VO_{2peak}.

While there were no within- or between-group changes in VO_{2peak}, the magnitude of improvement in W_{peak} was greater in the experimental group than in the control group following the intervention period in people with CF ($p = 0.017$). Recent data from an international multicentre study demonstrated that W_{peak} was a predictor of both survival and need for lung transplantation at 10-year follow-up (hazard ratio 0.969; 95% CI, 0.951 to 0.988) when controlling for age, sex, FEV_1, body mass index, CF-related diabetes and the colonisation of *Pseudomonas aeruginosa* [38]. This means that improving markers of exercise capacity such as W_{peak} is an important treatment goal of exercise training and that improvements in W_{peak} can be achieved with only 30 minutes of HIIT per week. An MCID for W_{peak} in people with CF is yet to be established. In people with COPD, the MCID for W_{peak} has been estimated at approximately 10 W [353]. The within-group median difference for the experimental group in the current RCT indicates that this improvement has the potential to be clinically important in people with CF.

The improvement in T_{lim} corroborates the improvement in physical functioning measured by the CFQ-R. Nevertheless, there were no between-group differences noted in overall HRQoL. This lack of improvement in other CFQ-R domains may reflect the small sample size and the intervention period (8 weeks) potentially being too short. In addition, there were no between-group improvements observed in other questionnaires, such as the BARSE and the PACES. We speculate that this may be due to the non-disease-specific nature of these questionnaires.

The HIIT program was well tolerated by participants, based on the results of attendance, completion and post-exercise muscle soreness. There were only a few reports of mild post-exercise muscle soreness. In addition to reporting participants' tolerance of the program, this is the first study to present reflections of people with CF on a HIIT program, with a particular focus on the facilitators and barriers to undertaking this mode of aerobic exercise. Four major themes were identified as facilitators from transcription and analysis of the debrief interviews. These themes comprised: (i) tolerability, (ii) commitment and flexibility, (iii) enjoyment, and (iv) the presence of a therapist during the HIIT sessions. There are some similarities between these themes and data reported in other studies. For example, one study in healthy but inactive men and women (n = 30, aged 21 ± 4 years) compared various modes of exercise (i.e. HIIT, sprint interval training and moderate intensity continuous exercise). High intensity interval training was the most enjoyed mode of exercise, and the largest proportion of participants (43%) reported preferring HIIT over the other modes of exercise (33% for moderate intensity continuous exercise and 23% for sprint interval training). Of note, the HIIT program had the highest tolerability with the lowest time commitment (i.e. 24 minutes for HIIT compared to 50 minutes for moderate intensity continuous exercise) [354]. The semi-structured interview themes provide further evidence that the HIIT program was well tolerated and enjoyable for the participants included in the study.

Participants identified some challenges to completing the HIIT program. On further analysis, these barriers appeared to be generic to exercise training, rather than specific barriers to undertaking HIIT. The themes related to barriers comprised: (i) perceived or actual lack of internal motivation to undertake exercise, (ii) the travel time associated with session visits, (iii) life commitments, and (iv) the impact of the disease process. Despite people with CF being a younger population than people with COPD, these barriers are similar to those reported previously in people with COPD undertaking pulmonary rehabilitation [355, 356]. Indeed, the translation of the cycling-based HIIT program to a walking- or running-based program, depending on the fitness level of participants, would alleviate some of the burden associated with attending an exercise facility and the need for equipment to undertake HIIT sessions.

The number of participants who reported increased symptoms indicative of a respiratory exacerbation was higher than expected by the research team. A possible explanation for this could be that, regardless of group allocation, participants had increased contact with the PhD candidate throughout the study period. Participants in the experimental group attended thrice-weekly for the HIIT sessions. Participants in the control group were contacted on a weekly basis to briefly discuss symptoms and exercise habits. These points of contact gave

both groups the opportunity to report symptoms more rapidly or frequently than they perhaps would have clinically.

Although adolescents were eligible to participate in the RCT, there was no uptake of the study in this age group. The youngest participant was 20 years of age.

6.5 Limitations

It is clear that recruiting participants into this RCT posed a significant challenge, and thus the sample size calculated *a priori* was not met. The reasons for insufficient recruitment were multi-factorial, comprising: (i) unwillingness of potential participants to undertake the testing and/or intervention sessions (i.e. due to being time-poor and travel distance), (ii) the clinical population being vulnerable to acute bouts of illness (i.e. respiratory exacerbations), and (iii) availability of the exercise testing equipment (i.e. exercise laboratory being used by all clinical populations at SCGH and increasing use by these populations during the study period). In addition, despite having the option (ethical and governance approval) of recruiting adolescents from PCH into the study, no adolescents chose to undertake the study. Upon discussion with the paediatric CF multidisciplinary team and consumer reference group, the difficulty of recruiting adolescents is commonly experienced in various other research studies at this site.

Another limitation to undertaking exercise testing and therefore recruitment into the RCT was logistics surrounding infection control precautions. To this effect, two people who were colonised with nontuberculous mycobacteria were not permitted to participate in the study due to the risk of cross-infection to other participants and other patients using the exercise laboratory.

Due to the nature of the intervention (i.e. HIIT versus weekly contact), it was not possible to blind the participants as to their group allocation [1].

An implication of the small sample size is that the debrief interview themes may not be generalisable to the wider population of people with CF. Additionally, each interview was undertaken, transcribed and analysed by the same investigator who supervised the HIIT program (the PhD candidate). This introduces the potential that participants may have refrained from reporting negative reflections on the program.

In order to reduce the attention bias, participants in the control group received weekly contact by a preferred method (phone call, SMS or emails). This regular contact may have led to ‘over reporting’ of symptoms indicative of a respiratory exacerbation because

participants were being asked to think about symptoms more regularly than would occur as part of true 'usual care'.

Finally, other than the HRQoL questionnaires (CFQ-R and the AweScore-CF), there are no CF-specific questionnaires to measure exercise self-efficacy, feelings of anxiety and depression, or exercise enjoyment. This is another limitation of the RCT because generic questionnaires are less responsive to changes than disease-specific questionnaires.

6.6 Conclusions

The findings of this study indicate that low-volume HIIT, completed up to three times per week for 8 weeks, is superior to usual care to improve exercise capacity in this group of people with CF. The results of this RCT should be interpreted with caution due to the small sample size, which is a major limitation to the generalisability of the results to the wider population of people with CF. Despite this limitation, the improvement in the primary outcome of exercise capacity (T_{lim}) was approximately three times the projected MCID in people with chronic respiratory conditions. In addition, the HIIT program was well tolerated and accepted by participants.

Participants allocated to the experimental group were able to achieve a 'work' intensity of well over 100% of their baseline W_{peak} during the final weeks of the HIIT program. Due to the novel and high intensity nature of the exercise undertaken in this RCT, participants were required to undertake the sessions with a physiotherapist present in a hospital setting. Considering the high tolerability of the HIIT program, albeit with fairly low uptake of participants into the study, exploration of the HIIT program to a home-based setting and into a walking/running-based program with monitoring via telehealth is warranted; this change in modality is likely to have a positive impact on uptake of the program, would limit the travel time and infection control risks associated with attending a hospital for training. In addition, it would avoid the need for additional equipment. Consideration would need to be given to facilitating the long-term adherence to a home-based program.

While the optimal dose of HIIT is unknown in people with CF and was not specifically explored in this program of research, a dose of 30 seconds of work interspersed with 30 seconds of rest, repeated six times, was sufficient to achieve a between-group improvement in the primary outcome of T_{lim}. As the pool of people with CF in Perth (Western Australia) was not sufficient to ensure adequate power to detect small differences between (or equivalence of) HIIT and other traditional modes of exercise (e.g. moderate intensity

continuous exercise), future studies seeking to compare training modes need to consider interstate/international collaborative trials.

CHAPTER 7

BEHAVIOUR CHANGE TECHNIQUES

Overview

This chapter comprises two parts. **Part 1** presents a systematic review on behaviour change techniques (BCTs) which have been reported in studies where interventions aimed at optimising physical activity or participation in exercise were delivered to young adults with chronic respiratory conditions. This review was published in the *Internal Medicine Journal* in October 2018 [270]. **Part 2** explores the BCTs and underlying psychological mechanisms of action employed within the randomised controlled trial (RCT) presented in Chapters 4 to 6. The systematic review (**Part 1**) is detailed first as many of the evaluation techniques used throughout are relevant to **Part 2**. The discussion pertains to both **Part 1** and **Part 2.**

7.1 Part 1

7.1.1 Research questions

The research questions were: in published work done in adolescents and adults with one or more chronic cardiorespiratory conditions, (i) which interventions aimed at optimising physical activity or participation in exercise appear to be ‘promising’ or ‘not promising’; and (ii) which BCTs could be identified and mapped from the ‘promising’ and ‘not promising’ interventions?

7.1.2 Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [357], and was prospectively registered with PROSPERO (CRD42017068892).

7.1.2.1 Eligibility criteria

Studies were eligible for inclusion in this review if: (i) the mean age of the sample was between 15 and 45 years; (ii) all participants had a chronic cardiorespiratory condition, which could include but was not limited to asthma, cystic fibrosis (CF), interstitial lung disease, congenital heart disease or cardiovascular disease; (iii) the study design was multi-arm with at least one participant group exposed to an intervention that incorporated BCTs included in the taxonomy (i.e. experimental group) [82] and one group acting as a control; and (iv) objective measures of physical activity or participation in exercise were collected before and after the intervention period via either wearable technology (e.g. accelerometer, inclinometer, heart rate monitor, portable metabolic monitor or step count monitor) or direct observation.

Studies were excluded if they used a cross-over or single-group design, or were published in a language other than English. Conference abstracts were also excluded.

7.1.2.2 Information sources and search

Studies were identified from computerised literature searches of CENTRAL, MEDLINE, PsychInfo, EMBASE (via OVID), PEDro (Physiotherapy Evidence Database) and CINAHL databases from their inception to October 2017. Clinical trials registries comprising ClinicalTrials.gov, the World Health Organization trials portal and the Australian New Zealand Clinical Trials Registry were searched in October 2017 for protocols meeting the eligibility criteria. Where eligible protocols were identified, authors were contacted to determine if the study had been published. The search strategy used for MEDLINE can be found in Appendix 1. This search strategy was adapted for use in other databases.

7.1.2.3 Study selection

Two review authors used Covidence software (Covidence, Melbourne, Australia) [358] to independently screen titles, abstracts and full papers identified by the search process against eligibility criteria. Disagreement between the two authors was resolved by discussion.

7.1.2.4 Data collection process

A data extraction template was developed *a priori*. A single review author undertook data extraction, the results of which were confirmed by other review authors. Data were extracted from eligible studies in relation to the following components:

Study characteristics: title, year, sponsorship, study design, number of participant groups, between-group differences at baseline and sample size.

Participant characteristics: participant groups, average age, cardiorespiratory condition and eligibility criteria.

Intervention: description (verbatim), number of interventions, monitoring and duration of sessions per week, intensity of physical activity/exercise prescribed, financial assistance received for study participation, additional support, and setting.

Comparator: as per intervention.

Outcomes: assessment time point, outcome measure and between-group differences.

Behaviour change techniques: extraction of BCTs from the interventions of included studies was conducted using Michie et al.'s BCT Taxonomy v1 [82]. The taxonomy comprises 16 major 'groups' of BCTs: Goals and planning, Feedback and monitoring, Social support, Shaping knowledge, Natural consequences, Comparison of behaviour, Associations, Repetition and substitution, Comparison of outcomes, Reward and threat, Regulation, Antecedents, Identity, Scheduled consequences, Self-belief, and Covert learning. Each of these groups incorporates a number of individual BCTs. For example, Group 1 (Goals and planning) encompasses nine individual BCTs: *goal setting (behaviour)* [1.1], *problem solving* [1.2], *goal setting (outcome)* [1.3], *action planning* [1.4], *review behaviour goal* [1.5], *discrepancy between current behaviour and goal* [1.6], *review outcome goals* [1.7], *behaviour contract* [1.8] and *commitment* [1.9]. Data were extracted following completion of the BCT Taxonomy v1 online training module and reviewed for quality by another review author who is experienced in the use of this taxonomy. A comprehensive list of the BCT Taxonomy v1 groups can be found in the supplementary material of the original article [82] and is included in Appendix 6.

7.1.2.5 Risk of bias

Cochrane's risk assessment tool [359], which reports on the methodological issues related to risk of bias in seven evidence-based domains: 'random sequence generation' and 'allocation

concealment' (selection bias), 'blinding of participants and personnel' (performance bias), 'blinding of outcome assessment' (detection bias), 'incomplete outcome data' (attrition bias), 'selective outcome reporting' (reporting bias), and 'other bias' was used. Studies were scored as being at a 'high', 'unclear' or 'low' risk of bias for each domain.

7.1.3 Data synthesis

7.1.3.1 Classification of interventions

Interventions were categorised as having a 'promising' or 'not promising' influence on the level of physical activity or participation in exercise by adolescents and adults with chronic cardiorespiratory conditions. Interventions were classified as 'promising' if, following the intervention period, there was a significant between-group increase in physical activity or exercise levels in favour of the experimental group. Interventions were classified as 'not promising' if, following the intervention period, no significant between-group differences were reported for physical activity or exercise levels [83, 360].

7.1.3.2 Identification and categorisation of behaviour change techniques

Specific components of each intervention were 'coded' as BCTs if sufficient detail was provided to validate the presence. The BCT was labelled with '++' if the authors were confident 'beyond reasonable doubt' that the BCT was present. If the BCT appeared to be present 'in all probability' from the intervention description, but there was insufficient detail, the BCT was coded as '+' [82]. For example, in one study, "Patients in the intervention group were called several times during the first 6 months of the study to check on their activity behaviour and, if necessary, to offer additional help" [271] was coded as *social support (unspecified)* with partial confidence ('+') because there was insufficient detail pertaining to the content of the conversation during the phone support. All 93 individual BCTs were considered for each of the interventions in the included studies. The BCTs were summarised by number and type.

7.1.4 Results

The search of electronic databases yielded a total of 7,692 records, of which 1,116 were duplicates. The titles and abstracts of the remaining records (n = 6,576) were screened against eligibility criteria. Following removal of ineligible records (n = 6,428), full texts of remaining studies were screened for eligibility. The main reasons for exclusion following full-text review were related to no objective measure of physical activity (n = 29) and the mean age of participants being > 45 or < 15 years (n = 104) (Figure 7.1).

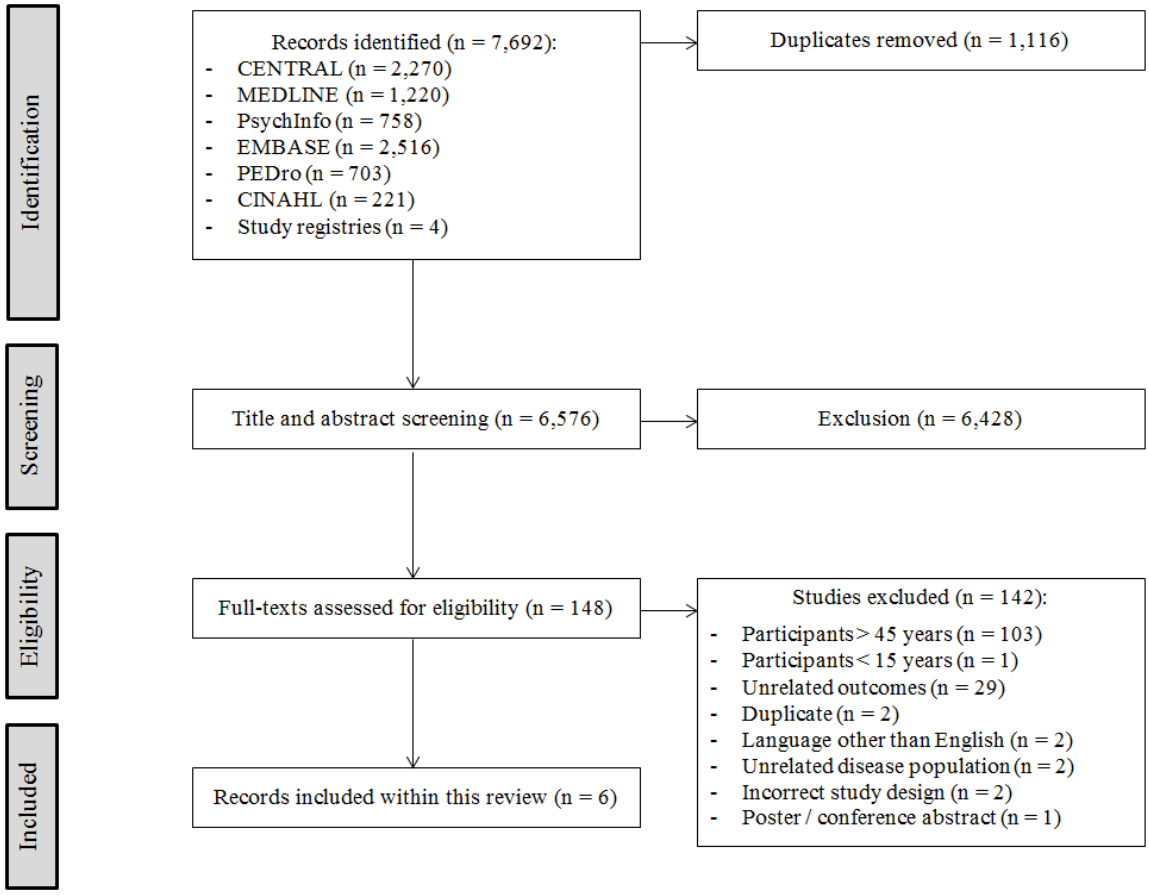

Figure 7.1 Search strategy and screening flow diagram

7.1.5 Characteristics of included studies

All six included studies were RCTs and had been conducted in Australia [361], Brazil [362], Germany [271], Ireland [363], the Netherlands [364], and Switzerland and Germany [365]. Across the included studies, there were 396 participants aged (mean ± standard deviation [SD]) 15 ± 3 years to 45 ± 12 years. Sample sizes ranged from 37 to143 participants, with 183 (46%) being female. Studies included people with asthma (n = 2) [361, 362], CF (n = 2) [271, 365] and congenital heart disease (n = 2) [363, 364].

7.1.5.1 Risk of bias

The quality of most included studies was poor to fair (Figure 7.2). No two studies were identical in terms of the risk of bias assessment. Performance bias (blinding of participants and personnel) was high across all studies and only one study was rated as having a low risk of detection bias (blinding of outcome assessor). Intention-to-treat analysis was reported in three studies [362, 363, 365]. Three studies reported not reaching the required sample size [271, 361, 363].

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other	**Overall quality**
Coelho (2017)* [362]	+	+	−	−	+	+	+	Moderate
Duppen (2015) [364]	?	?	−	−	+	+	?	Fair
Hebestreit (2010)* [271]	−	?	−	−	?	?	?	Poor
Kriemler (2013) [365]	−	−	−	+	+	−	?	Fair
Morrison (2013)* [363]	−	−	−	−	−	−	?	Poor
Scott (2013) [361]	+	+	−	−	+	−	?	Fair

Figure 7.2 Risk of bias summary

(+) Low risk of bias; (?) unclear risk of bias; (−) high risk of bias. '*' = 'promising' studies. Quality assessment: high = six to seven criteria met, moderate = four to five criteria met, fair = two to three criteria met, poor = one or less criteria met.

Allocation (selection bias)

Three studies [361, 362, 364] reported using an appropriately concealed random system to allocate participants into each group and were therefore judged as having low risk of selection bias. The remaining three studies [271, 363, 365] were judged as having a high risk of selection bias due to inadequate randomisation or allocation concealment.

Blinding (performance bias and detection bias)

The participants and personnel delivering the intervention were not blinded as to the participants' group allocation in any of the included studies and all studies were therefore rated as having a high risk of performance bias. Overall, blinding of the outcome assessors was poor across the included studies. One study [365] reported partial blinding of the outcome assessor (blinding for the primary outcome only). In the remaining studies, the outcome assessors were either not blinded [361, 362], or there was insufficient detail regarding the blinding of outcome assessors [271, 363, 364].

Incomplete outcome data (attrition bias)

Four of the included studies were rated as having a low risk of attrition bias related to incomplete outcome data [361, 362, 364, 365]. One study [271] was rated as having an unclear risk of bias due to inadequate information regarding follow-up assessments. That is, the reasons for loss to follow-up were outlined at the first follow-up assessment but not at subsequent assessment time points, and the reasons for drop-out were unclear from the analyses. One study [363] was rated as having a high risk of bias due to a higher rate of attrition, as well as no reasons provided for the loss to follow-up.

Selective reporting (reporting bias)

The detection of reporting bias was highly variable. Three studies [362, 364, 365] reported outcomes appropriately and were therefore rated as having a low risk of reporting bias. One study [363] was judged as having an unclear risk of bias due to reporting within-group differences rather than between-group differences. Two studies retrospectively registered their studies on clinical trials registries [361, 363].

Other

Other sources of bias within the included studies were generally low. However, two studies were rated as having an unclear risk of bias due to testing procedures [364] and financial support [271].

7.1.5.2 Interventions

Intervention delivery was highly variable in terms of frequency and duration of contact, the presence of a therapist, monitoring, intensity of the physical activity and/or exercise prescribed, support provided, location, and length of the intervention period (Table 7.1). Five studies implemented exercise training programs [271, 361, 363-365]. In three of these studies [271, 361, 363], promotion of physical activity was added to the exercise training program. One study focused on promotion of physical activity without an exercise training component [362]. The duration of interventions ranged from 10 weeks to 6 months. Interventions were conducted with a therapist fully present (n = 3) [361, 364, 365], not present (n = 1) [362] or partially present (n = 2) [271, 363]. In one of the interventions where the therapist was partially present [271], participants were asked to increase their participation in a sport of their choosing by 3 hours each week. For example, some participants undertook resistance training in a fitness centre (therapist present), other participants opted to complete independent endurance sports (cycling, jogging or swimming), and some chose to complete a mixture of these options. In the other intervention where the therapist was partially present [363], participants undertook group education sessions, but were provided with an independent program to complete at home to increase their activity.

Four of the six included studies had a two-arm design (i.e. intervention and control group) [271, 362-364], one study had a three-arm design (i.e. two intervention groups and a control group) [365], and one study had a four-arm design (i.e. three intervention groups and a control group) [361].

Table 7.1 Characteristics of interventions

Authors	Coelho (2017) [362]	Duppen (2015) [364]	Hebestreit (2010) [271]	Kriemler (2013) [365]	Morrison (2013) [363]	Scott (2013) [361]
Population	Asthma	Congenital heart disease	Cystic fibrosis	Cystic fibrosis	Congenital heart disease	Asthma
Description of intervention	All participants attended an individualised standardised education session. Intervention group: provided with a diary to register asthma exacerbations. Also provided with a step-based (walking) physical activity prescription plan with targets. Control group: provided with a diary to register asthma exacerbations.	Intervention group: provided with an aerobic exercise training program (aerobic dynamic cardiovascular training and a warm-up/cool-down). Control group: instructed to continue their normal daily life.	Intervention group: asked to increase sport activities (individualised); endurance-type activities or combined training (endurance and weights). Control group: asked to maintain a constant physical activity level.	Intervention group (1) (strength training): provided with a series of upper and lower body weight exercises. Intervention group (2) (aerobic training): provided with an aerobic training program based on individual preference. Control group: asked to maintain a constant physical activity level.	Intervention group: invited to attend activity day, which included a motivational interviewing style group, pros and cons of exercise, and visualisation techniques. Control group: asked to continue usual care.	Intervention group (1) (exercise intervention): provided with a gym membership and group personal training. The same gym was used by participants to ensure a comparable program. Designed by an exercise physiologist. Intervention group (2): provided with a dietary intervention ('control'). Intervention group (3) (combined group): completed exercise and dietary interventions.

Duration of the intervention period	12 weeks	12 weeks	6 months	6 months	6 months	10 weeks
Time	Both groups: 1 hour standardised education session. Intervention group: advised to increase physical activity to 5 times per week for > 30 minutes. Control group: advised to increase physical activity to 5 times per week for > 30 minutes.	Intervention group: 3 times per week for 1 hour. Control group: no change/no specific time commitment.	Intervention group: 3 times per week for 1 hour. Control group: no change/no specific time commitment.	Intervention groups: 3 times per week for 30 to 45 minutes for the first 6 months of the study. Control group: no change/no specific time commitment.	Intervention group: An education session and follow-up letter summarising discussions. Monthly follow-up. Control group: no change/no specific time commitment.	Intervention group (1 and 3): 1-hour personal training session, gym membership/program and daily step goal. Intervention group (2): ('control') seven 1-hour clinic visits and four 10-minute phone calls with a dietician.
Intensity of intervention	Each participant asked to commence walking at a moderate intensity (using talk test – explained). Progressive step-based goals.	10-minute warm-up and cool-down. 40 minutes of aerobic exercise at 60 to 70% maximal heart rate.	Below gas exchange threshold (equivalent heart rate).	Strength training: set by fitness centre staff. Weight increase by 5% per week if the participant could do > 9 repetitions. Anaerobic training: commenced at 65% VO_{2peak}.	Not specified.	Not specified.

Additional support	Weekly contact about asthma control and step count. Monthly clinic visits.	Physiotherapist present during intervention.	Activity counselling provided at baseline, 3 and 6 months (discussion of options about incorporating intense exercise into daily life and generation of an activity plan). Logistical support was provided (exercise supervision and guidance). Phone calls to monitor activity and offer additional help.	Intervention groups called once a month during the first 6 months of training to check adherence and provide support. After the first 6 months, patients in the intervention groups were encouraged to maintain their training, but no further steps were taken to increase adherence.	Not specified.	Phone consultation for dietary group and the combined group. Exercise group provided with information on physical activity recommendations and goals developed with the study dietician. They signed an informal contract.
Contact with investigators and monitoring provided to the intervention group(s)	Participants asked to fill out daily diary to monitor for exacerbation. Provided with pedometer to monitor step count.	Provided with heart rate monitor for exercise intensity.	Provided with heart rate monitor and advice on target range for endurance activities.	Fitness centre staff monitored attendance. Provided with heart rate monitor (anaerobic training only).	Monthly follow-up phone calls to discuss progress and problems.	Provided with pedometer to monitor step count.

Financial assistance	Not specified.	Not specified.	£200 was offered to participants to assist implementation/ maintenance of activity plan.	Access to a fitness centre (both intervention groups).	Not specified.	Gym membership provided. No other financial support provided.
Location	Community-based/ independent.	Not specified.	Variable (i.e. fitness centre or sports club).	Fitness centre (both intervention groups) or home (anaerobic training only).	Home/community-based.	Gym-based.

Abbreviation: VO_{2peak}: peak rate of oxygen uptake.

Interventions considered promising versus not promising (aim 1)

Of the six included studies [271, 361-365], half (n = 3) [271, 362, 363] were considered to have a 'promising' effect on physical activity or participation in exercise.

Behaviour change techniques across all studies (aim 2)

Nineteen (20%) of the 93 individual BCTs outlined in the BCT Taxonomy v1 were represented within the study interventions (Figure 7.3). The number of individual BCTs identified within each of the included studies ranged from two [364] to 10 [365], with (mean ± SD) 6 ± 3 BCTs described per study. The most commonly used BCTs across included studies were *goal setting (behaviour)* [indicated in Figure 7.3 as 1.1] (5/6 studies) and *action planning* [indicated in Figure 7.3 as 1.4] (5/6 studies). Eight BCTs were coded only once across the six studies: *problem solving* [indicated in Figure 7.3 as 1.2], *goal setting (outcome)* [indicated in Figure 7.3 as 1.3], *feedback on behaviour* [indicated in Figure 7.3 as 2.2], *information about health consequences* [indicated in Figure 7.3 as 5.1], *credible source* [indicated in Figure 7.3 as 9.1], *pros and cons* [indicated in Figure 7.3 as 9.2], *comparative imagining of future outcomes* [indicated in Figure 7.3 as 9.3], and *adding objects to the environment* [indicated in Figure 7.3 as 12.5].

Behaviour change techniques used in promising interventions

The most frequently used BCTs in interventions categorised as having a 'promising' effect on physical activity or participation in exercise were *goal setting (behaviour)* [indicated in Figure 7.3 as 1.1] and *action planning* [indicated in Figure 7.3 as 1.4]. Each of these BCTs were utilised on four occasions across three separate interventions [271, 362, 363]. Five BCTs were solely used in 'promising' interventions: *problem solving* [indicated in Figure 7.3 as 1.2], *information about antecedents* [indicated in Figure 7.3 as 4.2], *information about health consequences* [indicated in Figure 7.3 as 5.1], *pros and cons* [indicated in Figure 7.3 as 9.2], and *comparative imagining of future outcomes* [indicated in Figure 7.3 as 9.3]. Of the 24 occasions BCTs were used in 'promising' interventions, 22 were described in sufficient detail to validate their presence with complete confidence [++, 'beyond reasonable doubt']).

Behaviour change techniques used in not promising interventions

The most commonly coded BCT among the interventions with a 'not promising' effect on physical activity or participation in exercise was *goal setting (behaviour)* [indicated in Figure 7.3 as 1.1], which was identified and coded on four occasions by four interventions [361, 365]. On one of these occasions, the BCT could only be coded with partial confidence (+, 'in all probability') [361]. *Goal setting (outcome)* [indicated in Figure 7.3 as 1.3],

feedback on behaviour [indicated in Figure 7.3 as 2.2], *credible source* [indicated in Figure 7.3 as 9.1], and *adding objects to the environment* [indicated in Figure 7.3 as 12.5] were used only in 'not promising' interventions. Of the 27 occasions BCTs were used in 'not promising' interventions, 22 were described in sufficient detail to validate their presence with complete confidence [++, 'beyond reasonable doubt'].

Group	BCT identified	Coelho (2017) [362]	Hebestreit (2010) [271]	Morrison (2013) [363]	Duppen (2015) [364]	Kriemler (2013) [365]	Scott (2013) [361]
		Promising			**Not promising**		
Group 1: Goals and planning	Goal setting (behaviour) (1.1)	2 ++		++		2 ++	2 ++/+
Group 1: Goals and planning	Problem solving (1.2)			+			
Group 1: Goals and planning	Goal setting (outcome) (1.3)						+
Group 1: Goals and planning	Action planning (1.4)	++	2 ++	++		2 ++	++
Group 1: Goals and planning	Review behaviour goal (1.5)	++				2 ++	
Group 1: Goals and planning	Discrepancy between current behaviour and goal (1.6)	++				2 ++	
Group 2: Feedback and monitoring	Monitoring of behaviour by others without feedback (2.1)		++			2 ++	
Group 2: Feedback and monitoring	Feedback on behaviour (2.2)					++	
Group 2: Feedback and monitoring	Self-monitoring of behaviour (2.3)	++					2 ++
Group 2: Feedback and monitoring	Biofeedback (2.6)		++		++	++	
Group 3: Social support	Social support (unspecified) (3.1)		2 ++/+	++			+
Group 3: Social support	Social support (practical) (3.2)		2 ++			2 ++	+
Group 4: Shaping knowledge	Instruction on how to perform a behaviour (4.1)		++		++	++	
Group 4: Shaping knowledge	Information about antecedents (4.2)	++		++			
Group 5: Natural consequences	Information about health consequences (5.1)	++					
Group 9: Comparison of outcomes	Credible sources (9.1)						++
Group 9: Comparison of outcomes	Pros and cons (9.2)			++			
Group 9: Comparison of outcomes	Comparative imagining of future outcomes (9.3)			++			
Group 12: Antecedents	Adding objects to the environment (12.5)					+	
	Total	8	9	7	2	16	9

Figure 7.3 Behaviour change techniques coded within interventions

▓ BCT coded once within the study. ▉ BCT coded more than once within the study (the number in the box indicates number of occasions that the BCT was used). '++' indicates that reviewers were confident 'beyond reasonable doubt' that the BCT was present. '+' indicates that the BCT was present 'in all probability', but supporting information was lacking.

7.2 Part 2

Part 2 of this chapter is an extension of the RCT conducted in this program of research (described in Chapters 4 to 6). This part maps the BCTs and underlying psychological mechanisms of action employed within the HIIT intervention. The purpose of Part 2 is to understand the components of the intervention that sought to influence behaviour change.

The research question was: in people with CF who were randomly allocated to the experimental group of the RCT conducted in this research program, which BCTs and psychological processes were organically employed to optimise participation in the HIIT intervention?

7.2.1 Methods

Permission was sought from participants to audio-record HIIT sessions over the 8-week intervention period. The audio-recorder was placed within 1 metre of the participant and cycle ergometer. The audio-recordings were transcribed verbatim and analysed by the PhD candidate. Specifically, all BCTs that were evident during the HIIT sessions were coded using the BCT taxonomy [82] described in Part 1 of this chapter. Briefly, Michie et al.'s BCT Taxonomy v1 [82] comprises 16 major 'groups' of BCTs: Goals and planning, Feedback and monitoring, Social support, Shaping knowledge, Natural consequences, Comparison of behaviour, Associations, Repetition and substitution, Comparison of outcomes, Reward and threat, Regulation, Antecedents, Identity, Scheduled consequences, Self-belief, and Covert learning. Each of these groups incorporates a number of individual BCTs (93 individual techniques overall). Of note, to be considered a BCT, the component needs to be observable, able to be replicated, and designed to alter or direct a behaviour. For example, within the present study, the behaviour was optimising participation in the HIIT program. This behaviour could be demonstrated by observing the participants attendance at each individual HIIT session, completion of each individual HIIT session, and completion of at least 70% of the total sessions. The coding process of BCTs was reviewed for accuracy by another investigator who is experienced in the use of the BCT Taxonomy [82].

To link the psychological processes through which behaviour change occurs, or 'mechanism of action', to each BCT, a method developed in an expert consensus study was used [366]. Specifically, there are 26 mechanisms of action which have previously been found to have links to specific BCTs of the Michie BCT Taxonomy v1 [366]. These mechanisms are: knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory/attention/decision

processes, environmental context and resources, social influences, emotion, behavioural regulation, norms, subjective norms, attitude towards the behaviour, motivation, self-image, needs, values, feedback processes, social learning/imitation, behavioural cuing, general attitudes/beliefs, and perceived susceptibility/vulnerability [366]. For clarity, a table of these mechanisms accompanied by their definitions is available in Appendix 6.

7.2.2 Results

A total of 59 HIIT sessions were recorded overall, with seven participants contributing data over three (in the participant who had a motor vehicle accident) to 12 sessions. No technical issues were encountered during the audio-recording process.

The BCTs mapped within the RCT are presented in Table 7.2. Overall, 15 out of a possible 93 BCTs [82] were included within the HIIT intervention. Three BCTs were present on more than one occasion. Of the 18 occasions that a BCT was employed overall, the BCT could be mapped with a high level of confidence on 15 occasions.

Of 26 possible mechanisms of action [366], 12 (46%) were identified within the intervention of this study. Of these, feedback processes and goals were the most commonly linked psychological mechanisms (five links and four links to specific BCTs, respectively).

Table 7.2 Behaviour change techniques within high intensity interval training intervention

Target population: Experimental group (adults with cystic fibrosis [CF] who were allocated to undertake 8 weeks of high intensity interval training [HIIT])
Target behaviour: Optimise participation in HIIT program: (i) attendance at each individual HIIT session, (ii) completion of each individual HIIT session, and (iii) completion of at least 70% of the total sessions.
Target outcome: Increase exercise capacity as determined by time to symptom limitation (primary outcome) during a constant work rate cycle ergometry test (at program completion). 'Proxy' measures of exercise capacity or 'indices' of intensity were taken from the work rate achieved during HIIT sessions, as well as symptom scores and heart rate readings.

Description of intervention component	Behaviour change techniques identified	Confidence	MoA
When in attendance at the HIIT sessions, participants were asked to increase the intensity of exercise each week depending on what they were able to tolerate (based on their perceived level of leg muscle fatigue and breathlessness, as a proxy measure of increasing exercise capacity). Sessions commenced at 60% of the W_{peak} in week 1, with the aim of achieving 80% of the W_{peak} by the end of week 2 (lead-in phase), and as symptoms permit from week 3 to week 8 of the program.	Goal setting (behaviour)	2	Goals Intentions
	Graded tasks	2	Skills B. Cap
Participants were provided with detailed instructions to attend the physiotherapy department (at their preferred hospital location) two, and then three, times per week for 8 weeks to undertake each HIIT session. Information was also provided on parking options at the hospital location via a map (as required). The same physiotherapist was present for all HIIT sessions throughout the program. The participants were able to contact the physiotherapist by phone or email to discuss booking sessions, various aspects of the program and any issues	Action planning	2	–
	Instruction on how to perform the behaviour	2	Skills
	Social support (unspecified)	2	Social influences

encountered.			
Participants were provided with verbal and written (an information sheet) instructions on post-exercise muscle soreness and how to manage potential symptoms prior to undertaking their first HIIT session. The verbal instructions were reiterated weekly and participants were advised to inform the physiotherapist of any delayed symptoms related to the HIIT.	Information about health consequences	2	Knowledge PSV
Discussion occurred with participants prior to commencing each HIIT session regarding the previous intensity achieved (based on work rate, symptoms and heart rate) as well as the goal for this session. At the completion of each session, further discussion of the markers occurred in order to reflect on the intensity achieved during the session.	Review behaviour goal(s) Feedback on outcome(s) of behaviour	2 2	Goals Feedback processes
The intensity of exercise (in Watts, as a percentage of the participant's baseline level of fitness), and achievements of other participants (who had already completed the intervention period) were discussed with current participants to reflect on the progress they had made, in comparison to the progress of others that had been made at similar time points.	Social comparison	1	Social influences Normative beliefs Feedback processes

Participants were provided with verbal (by the physiotherapist) and visual (Watt display on the computer on the cycle ergometer) cues regarding how far they were through each interval, the intensity achieved during the interval and the time left for HIIT session. Observations (HR, SpO_2 and Borg scores, and Watts on the cycle ergometer) were monitored by the physiotherapist throughout each HIIT session and verbal feedback was provided by the physiotherapist to reassure the participant at regular time intervals on how they were responding to the session.	Biofeedback	2	Feedback processes
	Feedback on behaviour	2	
In order to convey the physiotherapist's confidence in the participant being able to achieve a specific intensity of exercise, participants were reminded about the intensity they were able to achieve in previous HIIT sessions, despite uncomfortable symptoms that may have been associated with the exercise. In addition, the physiotherapist provided positive reinforcement and encouragement when a particular intensity was achieved (i.e. based on Watts) despite the difficulty in achieving the behaviour (i.e. onset of leg muscle fatigue and breathlessness).	Social reward	2	Reinforcement Social influences Motivation
	Verbal persuasion about capability	1	Motivation
	Focus on past success	2	–

The participants were advised that to have 'completed' the intervention, they were required to attend at least 70% of sessions. The session count was discussed with the participant weekly in order to plan for the remaining sessions/weeks and set goals for the exercise intensity to aim for in the remaining weeks.	Goal setting (behaviour)	2	Motivation Goals Intentions
	Review behaviour goal(s)	2	Feedback processes Goals
	Feedback on behaviour	2	Feedback processes
If a participant missed a session(s), they were permitted to extend the program by a maximum of 2 weeks. This was outlined to the participant at the start of the program, and if they had to cancel a session for any reason (life commitments, being medically unwell etc.)	Restructuring the physical environment	1	Environment Cueing

Abbreviations: B. Cap: beliefs about capabilities, HR: heart rate, MoA: mechanism of action (processes which influence behaviour), PSV: perceived susceptibility and vulnerability, SpO_2: peripheral capillary oxygen saturation, W_{peak}: peak work rate. A '2' in the confidence column of the table indicates that the PhD candidate was confident 'beyond reasonable doubt' that the technique was present. A '1' in the confidence column indicates that the technique was present 'in all probability'.

Note: MoAs linked to BCTs have been included when there was > 80% agreement during expert consensus of a link being present [366, 367].

7.3 Discussion

The systematic review conducted in Part 1 of this chapter is the first to apply the BCT Taxonomy v1 [82] to interventions aimed at optimising physical activity, which may have included participation in exercise, in adolescents and younger adults with chronic cardiorespiratory conditions. Six studies met the inclusion criteria and most were of fair to poor quality. The three main findings of this systematic review were that: (i) only 20% of the individual BCTs outlined in the v1 Taxonomy were represented within the interventions of included studies; (ii) three of the six studies had interventions that had a 'promising' influence on physical activity or participation in exercise; and (iii) five BCTs (namely *problem solving*, *information about antecedents*, *information about health consequences*, *pros and cons* and *comparative imagining of future outcomes*) were solely used in 'promising' interventions.

The finding that few (20%) of the BCTs outlined in the v1 Taxonomy [82] were represented within the interventions of included studies supports earlier work, which reported a limited number of BCTs in studies aiming to optimise physical activity in adults with COPD [368] or implement home-based cardiac rehabilitation in adults with cardiac disease [369]. A recent systematic review on the use of BCTs by physiotherapists in interventions aimed at increasing physical activity has demonstrated that 'promising' interventions used more BCTs than 'not promising' interventions [370]. This finding contrasts with the current systematic review, which identified a comparable number of BCTs between 'promising' and 'not promising' interventions. One possible reason for this disparity is that this review only included RCTs, and the decision to classify interventions as 'promising' was the finding of significant between-group differences in objective measures of physical activity. In contrast, the earlier systematic review [370] included studies that provided lower levels of evidence (i.e. uncontrolled single-group studies with subjectively reported measures of physical activity).

Commonly used BCTs were similar between 'promising' and 'not promising' interventions and included *goal setting (behaviour)* and *action planning*. *Goal setting (behaviour)* is defined as "setting or agreeing on a goal defined in terms of the behaviour to be achieved, for example, agreeing on a weekly exercise target" [82]. *Action planning* is similar except that, in addition to defining a goal, explicit instruction is given regarding the context, frequency, duration and/or intensity of the behaviour. Of note, *action planning* was used in all of the 'promising' interventions, and two of the three 'non-promising' interventions. Notwithstanding these similarities in BCTs common to 'promising' and 'not promising'

interventions, there were two noticeable differences in the way they were applied: (i) specificity of the goal (i.e. promotion of physical activity rather than just participation in the exercise program), and (ii) length of intervention. That is, compared to 'not promising' interventions, which tended to focus solely on an exercise program, 'promising' interventions included promotion of physical activity, either alone [362] or in combination with an exercise program [271, 363]. For example, Morrison et al. [363] discussed ways to increase physical activity, and in the study by Hebestreit et al. [271], physical activity counselling and discussion of an activity plan were undertaken. Our data suggest that, when attempting to increase participation in physical activity, it is the embedding of specific instructions regarding the *execution* of this health behaviour (i.e. action planning) within an exercise training intervention that is needed to optimise success [371]. Additionally, the current study demonstrated that longer interventions seem to be more advantageous than shorter interventions to change physical activity behaviour in adolescents and adults with a chronic cardiorespiratory condition. That is, the majority of 'promising' interventions (2/3) were 6 months or longer in length, compared to an average of 12 weeks or less for the majority (2/3) of 'not promising' interventions. This finding is in agreement with results of a study of pulmonary rehabilitation in people with COPD that demonstrated that a 3-month intervention improved exercise capacity, muscle force and quality of life. However, physical activity only improved after 6 months of intervention [372]. Longer interventions may be more advantageous than shorter interventions because of the time it takes to implement physical activity BCTs and/or the time it takes for these BCTs to positively influence the target behaviour.

Several BCTs were described only within 'promising' interventions. Specifically, *problem solving*, which is categorised within the 'Goals and planning' group of the BCT Taxonomy v1 [82], was solely used in 'promising' interventions. This suggests that when attempting to change physical activity, it is important to offer *problem solving* together with *goal setting (behaviour)* and *action planning.* Given the magnitude of barriers for people with chronic cardiorespiratory conditions, identifying obstacles and potential solutions in advance is important for ongoing adherence to physical activity and exercise programs. Earlier work has also reported the value of highlighting behavioural 'norms' to participants, particularly in the context of goal setting [373, 374], and this is likely to explain why *information about antecedents* and *information about health consequences* were identified within 'promising' interventions. Another BCT used only in 'promising' interventions was *pros and cons*, whereby "a person is advised to identify and compare reasons for wanting (pro) or not wanting (con) to change a behaviour" [82]. This technique, commonly referred to in the literature as decisional balance, is an important element of behaviour adoption

[375], and positive decisional balance (i.e. higher perceived pros than cons) has been shown to strongly influence participation in physical activity [376]. Additionally, positive decisional balance may have a role in long-term participation in physical activity in people who are already active [377]. Finally, *comparative imagining of future outcomes,* or mental contrasting, was also used solely in 'promising' interventions. Similar to decisional balance, this technique emphasises the need for action towards a goal by considering a positive future achievement of a behaviour (e.g. completing physical activity for 30 minutes per day) despite negative barriers (e.g. motivation, inclement weather, competing time interests), and is particularly useful in adolescents and adults [378, 379]. Our finding that these BCTs were described in 'promising' interventions is supported by earlier work. For example, in a systematic review investigating the use of BCTs in cardiac rehabilitation programs [369], *information about health consequences* was only used by efficacious cardiac rehabilitation programs. Likewise, in another review investigating BCTs utilised by physiotherapists for physical activity interventions in people with non-communicable disease, *problem solving* and *information about health consequences* were only identified in interventions considered efficacious at improving physical activity [370].

Although this review used a comprehensive search strategy to find studies that met our eligibility criteria, the results should be interpreted with caution as the number of studies included was small and their quality was variable. Further, on several occasions, we were unable to code potential BCTs with any confidence due to insufficient detail reported for the intervention. The breadth of uncoded BCTs, techniques only being coded on a single occasion, and the heterogeneity and limited number of included studies reduces our confidence to conclude which BCTs are likely to be most useful to optimise physical activity in adolescents and adults with chronic cardiorespiratory conditions. The heterogeneity between studies was high due to the diversity of chronic cardiorespiratory conditions. While the focus of this thesis was primarily CF, a multitude of conditions were eligible for inclusion within this systematic review due to the underdeveloped literature base solely in this area of CF. The age range of 15 to 45 years was selected to represent a similar demographic to adolescents and adults with CF. This was because useful BCTs have the potential to differ between age groups. Moreover, studies were only included in the review if the measurement of physical activity was device-based or by direct observation. While device-based measures of physical activity are more robust than self-reported measures of physical activity [380], studies aiming to optimise physical activity or participation in exercise that utilised subjective measures of physical activity may have included BCTs which have not been used in the studies included in the current review.

Part 2 of this chapter sought to map the BCTs incorporated within the HIIT intervention. A novel approach has been taken to synthesise the BCTs and corresponding psychological mechanisms of action incorporated alongside a HIIT program in people with CF. To our knowledge, this is the first study to synthesise BCTs using an internationally recognised taxonomy in an exercise intervention in people with CF. Fifteen out of a possible 93 BCTs were mapped within the HIIT program. On most occasions (83%), BCTs were mapped with a high level of confidence. The current study included a similar number of BCTs to that reported in previous studies included in the systematic review conducted in Part 1 of this chapter [270]. The importance of the number of BCTs incorporated within a single intervention is contentious, with some studies suggesting that more techniques improve adherence to interventions, and other studies suggesting the contrary [270, 381-383]. It may not be the number of BCTs incorporated into interventions, but the combination of techniques used that is most effective. As such, the mapping of techniques should be interpreted with caution as their effectiveness may not be substantiated when prescribed independently. A key implication for future intervention design is the need to implement a systematic, rigorous process to articulate the problem (e.g. target behaviour(s), barriers and enablers) and create an intervention that addresses these issues. Intervention mapping, for example, is one approach that has gained reasonable traction.

The Consensus of Exercise Reporting Template (CERT) [384, 385] provides a guideline for the minimum level of detail required when reporting exercise interventions. This template comprises 16 items, for example, equipment requirements, exercise prescription and progression, level of ‘supervision’, and exercise setting. Despite this thorough template, similar templates for the reporting of BCTs are currently lacking. As a result, BCTs are seldom reported in sufficient or any detail in studies involving exercise interventions, and, to our knowledge, this is the first study to report the specific BCTs of an exercise intervention in people with CF. Data on BCTs are particularly relevant for therapists planning to develop or replicate the HIIT intervention in clinical practice.

Use of the term ‘supervision’ is common in exercise interventions to describe the completion of sessions with a therapist present (‘supervised’) or not (‘unsupervised’). The limitation of this term is that the specific undertakings of the therapist during each training session are rarely outlined in adequate detail in published studies. As such, evaluation of BCTs is challenging, and the omission of these details limits the replication and translation of the intervention into clinical practice. The undertakings of part 2 ‘quantify’ the supervision component of the HIIT program using BCTs. Therefore, it would be possible for clinicians and researchers to replicate the intervention accurately in clinical practice and future studies.

7.3.1 Conclusion

A relatively small number of potential BCTs were identified within interventions aiming to optimise physical activity in adolescents and adults with a chronic cardiorespiratory condition. Although there was some overlap in the BCTs described within 'promising' and 'not promising' interventions, BCTs such as *problem solving*, *information about antecedents*, *information about health consequences*, *pros and cons* and *comparative imagining of future outcomes* were only used in those studies that reported 'promising' interventions. Despite the growing consensus surrounding the importance of BCTs in changing health behaviours, this systematic review has demonstrated that details of specific interventional BCTs may be underreported, or BCTs may not be considered fully when devising interventions in adolescents and adults with chronic cardiorespiratory conditions. At present, there is limited evidence to support the use of individual BCTs, or specific combinations of BCTs, over others within interventions aiming to optimise physical activity in this population.

The mapping of BCTs present within the RCT conducted for this program of research highlights the numerous diverse components of the HIIT intervention, including the specific tasks of therapist supervision, designed to facilitate changes in behaviour. Ongoing stringent reporting of interventions and consideration of BCTs will allow for more precise and meaningful evidence synthesis in future systematic reviews. In addition, the reporting of BCTs has the capacity to optimise participation in exercise training programs in future research and clinical practice.

CHAPTER 8

SUMMARY AND CONCLUSIONS

Overview

This program of research included four studies, and the current PhD thesis comprises eight chapters. The overall aim of this program of research aimed to explore approaches to exercise testing and training in adults with chronic respiratory conditions, in particular, cystic fibrosis (CF). Chapters 1 provides the Introduction to the program of research. Chapter 2 presents the Literature Review. Within the Literature Review, a **narrative review and meta-analysis** was undertaken to explore the effects of high intensity interval training (HIIT) on exercise capacity in people with chronic respiratory conditions. Where there was a dearth of literature in the CF population, data collected in other chronic respiratory conditions were reviewed. Chapter 3 was a **survey** undertaken to report the exercise testing and exercise training procedures in CF centres in Australia and New Zealand. Chapters 4 to 6 was a **randomised controlled trial** (RCT) undertaken to evaluate the effects of HIIT on exercise capacity, health-related quality of life (HRQoL), exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. The methods of this RCT have been published in a peer-reviewed journal and are available in Chapter 4. Baseline data collected as part of the RCT were used to compare the physiological and symptom responses of people with CF to two different **laboratory-based exercise tests**. The findings of this comparison are presented in Chapter 5, and the **main results** and discussion of the **RCT** are

presented in Chapter 6. Chapter 7 (Part 1) presents a **systematic review** conducted to classify interventions aimed at optimising participation in physical activity as 'promising' or 'not promising' in people aged 15 to 45 years with chronic cardiorespiratory conditions, and categorise the behaviour change techniques (BCTs) within these interventions. Finally, the mapping of the **BCTs** employed within the RCT conducted as part of this research program are reported in Chapter 7 (Part 2).

8.1 Chapter 2, Part 5

The final section of Chapter 2 presented an invited narrative review with meta-analysis, which was published in *BMC Sports Science, Medicine and Rehabilitation* in March 2020 [87]. The question answered within the invited review was: what is the evidence for the effects of land-based whole-body HIIT on exercise capacity in adults living with chronic respiratory conditions, including people with chronic obstructive pulmonary disease (COPD), CF, non-CF bronchiectasis, asthma, interstitial lung diseases (ILDs) and non-small cell lung cancer (NSCLC)? Where possible, for each condition, studies that explored the effectiveness of HIIT compared to usual care (i.e. no exercise) were presented separately to those that compared the effects of HIIT with continuous exercise training. Meta-analyses from existing reviews were updated for COPD. Due to a scarcity of data reporting the effects of HIIT on exercise capacity in other chronic respiratory populations, it was not possible to undertake further meta-analyses.

Two studies compared the effect of HIIT, embedded within a 12-week pulmonary rehabilitation program, *versus* no exercise (i.e. the comparison was a control group that did not undergo exercise training or pulmonary rehabilitation), on measures of exercise capacity in people with COPD [290, 291]. As both studies explored the use of HIIT provided within a pulmonary rehabilitation program, which included resistance exercises and education, the gains in exercise capacity cannot be directly attributed solely to the HIIT. The meta-analysis demonstrated no clear advantage for HIIT compared to continuous exercise on W_{peak} (mean difference [MD] 95% confidence interval [CI] 0.73 W [CI −3.84 to 5.21]; nine studies) or VO_{2peak} (MD −0.13 $L \cdot min^{-1}$ [−0.05 to 0.03]; eight studies) [35, 87].

In people with CF, non-CF bronchiectasis and ILDs, there are currently no published RCTs evaluating the effects of HIIT compared to usual care or to moderate intensity continuous exercise. Nevertheless, in people with CF and ILDs, there were data to show that HIIT was well tolerated [34, 60, 318]. High intensity interval training in people with asthma is somewhat contentious, owing to the variable effects on bronchoconstriction and symptoms during exercise. Data from one RCT supports the use of pre-operative HIIT (compared to

usual care) in people with NSCLC to increase exercise capacity; that is, the HIIT group demonstrated greater improvements than the control group in VO_{2peak} on completion of the training program (MD 4 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 2 to 6) [321]. However, the effects of HIIT compared with moderate intensity continuous exercise in people with NSCLC are unknown.

Some studies (particularly those with shorter work to rest intervals) have shown superior improvement in exercise capacity (workload) with comparable improvements in cardiorespiratory fitness (VO_{2peak}), favouring HIIT in people with COPD. Additionally, 70% of studies included within this narrative review prescribed interventions whereby the total volume of work was matched between the HIIT and continuous exercise interventions. As such, future studies, particularly in people with COPD, are needed to determine whether HIIT, during which a smaller total training load is prescribed, can produce comparable or superior benefits in exercise capacity and cardiorespiratory fitness to continuous exercise. This review emphasises the need for large RCTs to investigate the effects of HIIT compared to usual care and HIIT compared to moderate intensity continuous exercise in most chronic respiratory populations.

8.2 Chapter 3

This chapter presented the methodology, results and discussion of a survey. This survey was published in the *Internal Medicine Journal* in August 2019 [162]. The aim of this survey was to determine the extent and scope of, and importance placed on, exercise testing and training within CF centres across Australia and New Zealand, for which there were no published data prior to this survey being undertaken. Specifically, the survey sought to explore differences in: (i) the utility of annual exercise testing; (ii) the nadir peripheral capillary oxygen saturation (i.e. cut-off value), below which testing and training would be terminated (or rests imposed); and (iii) the proportion of CF centres that provide an exercise training program.

The response rate of this survey was 80% (32/40 centres). The main findings related to current exercise testing and training practices in Australian and New Zealand CF centres were: (i) the majority of CF centres (n = 21/32) do not undertake laboratory-based exercise tests and, if performed, these tests are generally undertaken on the minority of patients; (ii) almost all CF centres (n = 28/32) undertake field-based exercise testing on at least half of their patients annually; (iii) participation in physical activity/exercise is discussed by at least one health professional in the CF team at every clinic appointment and/or at annual review; (iv) most centres (n = 24/32) offer some form of exercise training program to patients, though uptake of these programs is considerably limited by space, staffing and infection control precautions; and (v) a large proportion of centres do not have a cut-off value for

peripheral capillary oxygen saturation below which exercise testing and training would be interrupted or ceased. This survey highlighted the variability surrounding exercise testing and training practices across Australia and New Zealand and can be used as a benchmark of current practice.

There were a number of limitations to this survey. On a few occasions, the survey was completed by a member of the team who may not have been directly involved in exercise testing and training practices. Additionally, some respondents may have been involved in exercise testing, but not exercise training and vice versa, which may reduce the accuracy of the results. To limit the impact of this, respondents were encouraged to discuss questions with their colleagues if they were unsure of an answer. Respondents were permitted to provide multiple responses, or no response (if their centre did not undertake exercise testing and training), for questions related to reasons for, limitations to performing, and importance placed on exercise testing and training. As smaller centres that did not undertake exercise testing or training were not required to answer questions regarding limitations to performing exercise testing and training, the data on limitations are most likely to reflect those experienced by large centres.

8.3 Chapter 4

The methodology of the single-blinded RCT conducted as part of this program of research was outlined in Chapter 4. This study protocol was published in *BMC Sports Science, Medicine and Rehabilitation* in November 2018 [61].

The specific research question answered in this chapter was: in people with CF, what was the effect of an 8-week low-volume HIIT program, compared with weekly contact and no formal exercise training, on exercise capacity (primary outcome), HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment (secondary outcomes)? Secondary research questions also answered were: in people with CF who were allocated to the experimental group of the RCT, (i) what proportion of participants developed post-exercise quadriceps femoris muscle soreness each week during the 8-week HIIT program, and how severe was this symptom; (ii) how well did the participants tolerate the HIIT program; and (iii) what were the participants' reflections on the facilitators and barriers following the HIIT program?

After providing written informed consent and completing an initial (i.e. baseline) assessment period, participants were randomised to the experimental group, or the control group, and completed an 8-week intervention period. On completion of the intervention period, those in the experimental group were invited to attend a 'debrief' audio-recorded interview and participants in both groups completed a follow-up assessment period.

During the intervention period, both groups received usual care (e.g. medication, airway clearance techniques). Those allocated to the experimental group also participated in HIIT sessions two to three times per week. Sessions were audio-recorded and overseen by the same physiotherapist (PhD candidate). Those in the control group were contacted weekly by the PhD candidate and asked about their level of exercise participation, symptom changes (if any) and whether they had any contact with their CF team.

8.4 Chapter 5

Chapter 5 presented an opportunistic comparison of physiological and symptom responses during the two cycle ergometry tests conducted as part of the baseline assessments for the RCT. A condensed version of the analyses was submitted for publication as a brief report in February 2020. This study sought to answer the following research questions: in adults with CF, (i) how do the physiological and symptom responses during a constant work rate cycle ergometry test compare to those elicited during a maximal incremental ramp-based cycle ergometry test; and (ii) what are the limits of agreement of peak measures during the two cycle ergometry tests?

This is the first study in adults with CF that has demonstrated trivial differences in the end-test exercise responses between ramp-based and constant work rate cycle ergometry tests. For instance, the median difference (95% CI) in peak rate of oxygen uptake (VO_{2peak}) was 1 $mL \cdot kg^{-1} \cdot min^{-1}$ (−1 to 2). Although the constant work rate test was shorter in duration (288 seconds (241 to 304)), it elicited similar peak responses to the ramp-based test. The results of this study provide evidence that the constant work rate cycle ergometry test, when conducted at 80% of the peak work rate (W_{peak}), elicits peak physiological and symptom responses. Bland–Altman plots show that the differences in measures of VO_{2peak}, peak minute ventilation (V_{Epeak}) and maximal heart rate (HR_{max}) were not systematic. The limits of agreement can be used to help interpret individual responses. That is, for any individual, when the magnitude of change in VO_{2peak}, V_{Epeak} and HR_{max} exceeds their respective limit of agreement, we can be 95% confident that the difference was not simply due to the error associated with using a different protocol on a different day. The median [IQR] time to symptom limitation (T_{lim}) for the constant work rate test (252 seconds [222, 306]) was within

the recommended timeframe of 180 to 480 seconds for a baseline test, indicating that the prescribed work rates were likely to be markedly above the critical power [348]. Therefore, for clinicians prescribing exercise at an intensity approaching or equivalent to 80% of the W_{peak} in a non-laboratory-based setting, the presence of a therapist and monitoring of physiological response should be considered, particularly during the initial stages of exercise prescription and progression of exercise intensity.

The results of this study would be strengthened by recruiting a larger sample of participants. Had this study been conducted as a standalone study (i.e. not as a component of an RCT), it is possible that a greater number of participants would have enrolled. In addition, since the planning of this program of research, ramp-based cycle ergometry tests with supramaximal verification have gained momentum as a method to confirm results of VO_{2peak}, among other important measures of cardiorespiratory fitness and performance. These tests are likely to be a superior approach to measuring cardiorespiratory fitness in future research, compared to testing without supramaximal verification [163, 350]. Finally, there are a number of limitations to undertaking laboratory-based CPETs in clinical practice for people with CF. These include their cost, time and personnel-intensive nature, and space requirements. As such, the uptake of these tests in CF centres is limited [40, 41, 162].

8.5 Chapter 6

This chapter presented the main results and discussion of the prospective single-blinded RCT. This is the first RCT to evaluate the effects of 8 weeks of thrice-weekly HIIT on exercise capacity, HRQoL, exercise self-efficacy, feelings of anxiety and depression, and exercise enjoyment in people with CF. This RCT demonstrated that 8 weeks of low-volume HIIT produced greater magnitude of change in exercise endurance capacity and W_{peak} over and above the magnitude of change by continuing usual care in people with CF (between-group difference $p = 0.017$). Improvements in exercise endurance capacity and W_{peak} were demonstrated despite the time commitment of the HIIT program being only 30 minutes per week. These findings of a low-volume HIIT program being effective are novel in people with CF. Notably, the between-group improvement in W_{peak} after 8-weeks of HIIT, favouring the experimental (HIIT) group, has important prognostic value in people with CF [38]. Participants allocated to the experimental group also demonstrated a greater magnitude of change (improvement) in the physical functioning domain of the Cystic Fibrosis Questionnaire Revised than the control group (between-group difference $p = 0.03$). There were uncertain effects for other outcomes. The findings of this RCT should be interpreted

with caution due to the small sample size, which is a major limitation in the generalisability of the results.

Further to the effects on endurance exercise capacity, the HIIT sessions were well tolerated by participants, with only a few reports of mild-severity post-exercise muscle soreness, and high rates of attendance and completion among participants allocated to the experimental group. Moreover, participants did not experience any adverse events during testing or HIIT sessions throughout the study period.

The HIIT program was conducted on a commercially available cycle ergometer. Additionally, the prescription and progression of the program using work rate (in Watts), and taking into account the participant's level of symptoms, is a feasible and achievable method to prescribe a program in clinical practice.

It is clear that recruiting participants into this RCT posed a significant challenge, and thus the sample size calculated *a priori* was not met. The reasons for insufficient recruitment were multi-factorial, comprising: (i) unwillingness of potential participants to undertake the testing and/or intervention sessions (i.e. due to being time-poor and travel distance), (ii) the clinical population being vulnerable to acute bouts of illness (i.e. respiratory exacerbations), and (iii) availability of the exercise testing equipment (i.e. exercise laboratory being used by all clinical populations at SCGH and increasing use by these populations during the study period).

Furthermore, other than the HRQoL questionnaires (CFQ-R and the AweScore-CF), there are no CF-specific questionnaires to measure exercise self-efficacy, feelings of anxiety and depression, or exercise enjoyment. This is another limitation of the RCT because generic questionnaires are less responsive to changes than disease-specific questionnaires.

The findings of this RCT warrant further research. Due to the novel and high intensity nature of the exercise training program prescribed for people with CF who took part in this RCT, participants were required to undertake the sessions in a hospital setting under the supervision of a physiotherapist. Considering the high tolerability of the HIIT program, albeit with fairly low uptake of participants into the study, exploration of the HIIT program to a home-based setting and into a walking/running-based program with monitoring via telehealth is warranted; this change in modality is likely to have a positive impact on uptake of the program, would limit the travel time and infection control risks associated with attending a hospital for training. In addition, it would avoid the need for additional equipment. Consideration would need to be given to the long-term adherence to a home-based program. Additionally, while the optimal dose of HIIT is unknown in people with CF,

a dose of 30 seconds of 'work' interspersed with 30 seconds of 'rest', repeated six times, was sufficient to achieve a between-group difference, favouring the experimental group, in the primary outcome of T_{lim}. As the pool of people with CF in Perth (Western Australia) is not sufficient to ensure adequate power to detect small differences between (or equivalence of) HIIT and other traditional modes of exercise (e.g. moderate intensity continuous exercise), future studies seeking to compare training modes need to consider interstate/international collaborative trials. Finally, consideration of individual facilitators of and barriers to exercise is important both clinically and in future research.

8.6 Chapter 7

This chapter comprised two parts. Part 1 presented a systematic review on BCTs that have been used to optimise participation in exercise in young adults with chronic respiratory conditions. This review was published in the *Internal Medicine Journal* in October 2018 [270]. Part 2 explored and mapped the BCTs employed within the RCT conducted as part of this program of research.

Part 1

This systematic review [270] was the first to apply the BCT Taxonomy v1 [82] to interventions aimed at optimising physical activity, which may have included participation in exercise, in adolescents and younger adults with chronic cardiorespiratory conditions. Six studies met our inclusion criteria and most were of fair to poor quality. The three main findings of this systematic review were that: (i) only 20% of the individual BCTs outlined in the v1 Taxonomy were represented within the interventions of included studies; (ii) three of the six studies had interventions that had a 'promising' influence on physical activity or participation in exercise; and (iii) five BCTs (namely *problem solving*, *information about antecedents*, *information about health consequences*, *pros and cons* and *comparative imagining of future outcomes*) were solely used in 'promising' interventions. Despite the growing consensus surrounding the importance of BCTs in changing health behaviours, this systematic review demonstrated that details of specific interventional BCTs may be underreported, or BCTs may not be considered fully when devising interventions in adolescents and adults with chronic cardiorespiratory conditions. At present, there is limited evidence to support the use of individual BCTs, or specific combinations of BCTs, over others within interventions aiming to optimise physical activity in this population.

Part 2

Part 2 of Chapter 7 sought to map the BCTs incorporated within the HIIT intervention of the RCT conducted as part of this program of research. A novel approach was taken to synthesise the BCTs and corresponding psychological processes through which behaviour change occurs, or 'mechanism of action' [366], incorporated alongside a HIIT program in people with CF.

Fifteen out of a possible 93 BCTs were mapped within the HIIT program. Three of these BCTs were mapped on more than one occasion (i.e. 18 uses of these BCTs overall). The current study included a similar number of BCTs to that reported in previous studies included in our systematic review (described above) [270] that investigated physical activity and participation in exercise training in young people with a chronic respiratory condition. The importance of the number of BCTs incorporated within a single intervention is contentious, with some studies suggesting that more techniques improve adherence to interventions, and other studies suggesting the contrary [270, 381-383]. It may not be the number of BCTs incorporated into interventions, but the combination of techniques used that is most effective. Behaviour change techniques have seldom been reported in sufficient or any detail in studies involving exercise interventions, and, to our knowledge, this is the first study to report the specific BCTs of an exercise intervention in people with CF. The presentation of the BCTs employed within the HIIT program will facilitate its replication, which is particularly relevant for therapists planning to develop or replicate the HIIT intervention in clinical practice.

8.7 Summary and future directions

Considering the data collected during this program of research, there are a number of novel and important findings. First, there is a dearth of research investigating the effects of HIIT in most chronic respiratory populations. Considering the strong physiological rationale for HIIT, this finding is surprising and disappointing for people with chronic respiratory conditions. This gap has been partially filled by the RCT conducted within this program of research, which demonstrated that 8 weeks of low-volume HIIT undertaken on a cycle ergometer is likely to be beneficial compared to usual care (no formal exercise training) in people with CF. The main purpose of this study was to investigate an exercise training program with a lower time burden (30 minutes per week) than what is recommended in clinical guidelines for people with CF (i.e. 30 to 60 minutes of aerobic exercise training on most days of the week). One of the main limitations to the uptake and prescription of HIIT in the clinical setting may be associated with the limited ability to undertake cardiopulmonary exercise tests in order to accurately prescribe the work and rest increments of HIIT. This lack

of uptake of laboratory-based exercise tests has been highlighted in the survey of current practices of exercise testing and training in CF centres across Australia and New Zealand. Considering the wide use of field-based exercise tests in people with CF, investigation into an alternative method to accurately prescribe HIIT from these tests in clinical practice would be warranted in people with CF. Uptake of the HIIT program was a substantial challenge. To partially alleviate this challenge in future studies, translation of the HIIT program into the home environment, with supervision provided by a therapist during periods of exercise prescription and progression of intensity, has the potential to influence uptake. The supervision component could be delivered face to face and/or via a telehealth platform. Future studies seeking to compare HIIT to moderate intensity continuous exercise need to consider interstate/international collaborative trials to ensure adequate power. The constant work rate cycle ergometry test has been seldom used in people with CF. When conducted at 80% of the W_{peak}, data from this program of research supports the stability and responsiveness of the constant work rate cycle ergometry test, despite the test being able to elicit similar responses to a maximal incremental ramp-based cycle ergometry test. Finally, there is a scarcity of implementation, and more likely reporting, of BCTs to optimise physical activity and/or participation in exercise training in studies of people with chronic cardiorespiratory conditions. As a result, there is likely to be difficulty replicating exercise interventions accurately in clinical practice. While strong consideration is given to the precise number of sets, repetitions and intensity of exercise training programs, BCTs should be a similarly important and integrated component of exercise prescription in future studies. Ongoing accurate reporting and synthesis will establish the extent to which BCTs play a role in the longevity of changes in health outcomes.

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APPENDICES

Appendix 1

Search strategy: MEDLINE (Ovid)

Search string	Search number	Search term	Search type
1	1	Chronic lung disease	Keyword
	1	Lung diseases	MeSH
	2	Chronic lung condition	Keyword
	3	Chronic pulmonary disease	Keyword
	4	Chronic heart disease	Keyword
	4	Heart diseases	MeSH
2	5	Physical activit*	Keyword
	5	Exercise therapy	MeSH
	6	Exercise	Keyword
	6	Exercise	MeSH
	7	Resistance training	Keyword
	7	Resistance training	MeSH
	8	Aerobic training	Keyword
	9	Endurance training	Keyword
	9	Physical endurance	MeSH
3	10	1 or 2 or 3 or 4	
	11	5 or 6 or 7 or 8 or 9	
	12	10 and 11	
	13	Limit 12 to English language and humans	
	14	Limit 13 to adolescents or young adults or adults	

Appendix 2

Exercise testing and training survey

EXERCISE TESTING AND TRAINING PATTERNS IN AUSTRALIAN AND NEW ZEALAND CYSTIC FIBROSIS CENTRES

Thank you for participating in this survey.

The purpose of this survey is to investigate the practice patterns and importance placed on exercise testing and training in Australian and New Zealand cystic fibrosis (CF) centres. This survey has been adapted from the work of others [1, 2].

Please answer the below questions to the best of your ability.

Section 1: Demographic Details

1. **Name and location of CF centre:**

   _____

   _____

2. Tick one: Adult centre □ Paediatric centre □ Mixed centre □

3. **Total number of patients currently managed in the CF centre:**

   _____

4. **Professional role of questionnaire respondent:**
   Physiotherapist □
   Exercise physiologist □
   Nurse □
   Doctor □
   Other (please list):

   _____

5. **Years of experience working with people with CF**:

   _____

Section 2: Laboratory-based Exercise Testing

6. **Does your centre undertake laboratory-based exercise testing in people with CF?** Yes/No (if no, participant is to skip section)

7. **Please outline the laboratory-based exercise testing equipment readily available in your centre** (tick all that apply):
   Pulse oximeter □
   Treadmill □
   Cycle ergometer □

Electrocardiogram □
Metabolic cart □
None of the above □
Other □ (please list below):

_____

8. **Please outline the type of laboratory-based exercise tests used routinely within your centre** (tick all that apply):
   Laboratory-based tests:
   - Treadmill test □
   - Cycle ergometry test □
   - Other □ (please list below):

_____
_____
_____

9. **Please outline the laboratory-based exercise protocol(s) that are most commonly used (space provided for additional detail):**
   Ramp □
   Step-wise □
   Other □ (please list below):

_____
_____
_____

10. **Reason(s) for conducting laboratory-based exercise tests** (tick all that apply):
    Annual review □
    Patients report reduced exercise tolerance □
    Pre-transplant □
    To investigate the effect of a therapeutic intervention □
    For exercise prescription □
    Research □
    Other (please list below):

_____
_____
_____

11. **Please provide the number of laboratory-based exercise tests completed in the preceding 12 months:**
    The minority (0 to < 20%) □
    Under half (20 to < 50%) □
    About half (50 to < 70%) □
    More than half (70 to < 100%) □
    Almost all □
    Unsure □

12. **Who usually conducts the laboratory-based exercise tests?**
    Physiotherapist □
    Exercise physiologist □
    Respiratory scientists □
    Nurse □
    Doctor □

Other (please list):

_____

13. Does your centre have a protocol regarding the level of oxygen desaturation permitted during laboratory-based exercise testing?

Yes – test ceased at < 90% SpO_2 □
Yes – test ceased at < 85% SpO_2 □
Yes – test ceased at < 80% SpO_2 □
No specific criteria □
Unsure □

14. Please comment of the availability of personnel to conduct laboratory-based exercise tests:

Always available □
Usually available □
Sometimes available □
Sporadically available □
Rarely available □
Not applicable □

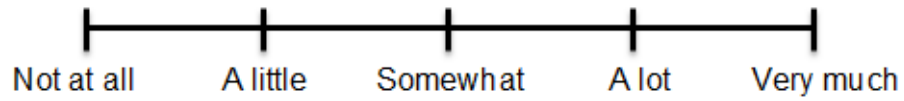
15. Please outline the main limitation to laboratory-based exercise testing being undertaken in your centre:

Staffing availability □
Staff training □
Equipment limitations □
Equipment availability □
Not viewed as importance in our centre □
Other (please outline) □
No limitation □

16. What do you believe, if anything, would enhance laboratory-based exercise testing in the centre? (i.e. personnel, equipment, space)

_____
_____
_____
_____

17. Please rate how important laboratory-based exercise testing is to your centre using this scale:



Section 3: Field-based Exercise Testing

18. Does your centre undertake field-based exercise testing in people with CF? Yes/No (if no, participant is to skip section)

19. Please outline the field-based exercise testing equipment readily available in your centre (tick all that apply):

Pulse oximeter □
Treadmill □
Cycle ergometer □

Electrocardiogram □
None of the above □
Other □ (please list below):

20. Please outline the type of field-based exercise tests used routinely within your centre (tick all that apply and space is provided for additional detail):

6 Minute walk test □
Incremental shuttle walk test □
Step test □
Endurance shuttle walk test □
Other □ (please list below):

_____

_____

_____

21. Reason(s) for conducting field-based exercise tests (tick all that apply):

Annual review □
Patients report reduced exercise tolerance □
Pre-transplant □
To investigate the effect of a therapeutic intervention □
For exercise prescription □
Research □
Other (please list below):

_____

_____

22. Please provide the number of field-based exercise tests completed in the preceding 12 months:

The minority (0 to < 20%) □
Under half (20 to < 50%) □
About half (50 to < 70%) □
More than half (70 to < 100%) □
Almost all □
Unsure □

23. Does your centre have a protocol regarding the level of oxygen desaturation permitted during field-based exercise testing?

Yes – test ceased at < 90% SpO_2 □
Yes – test ceased at < 85% SpO_2 □
Yes – test ceased at < 80% SpO_2 □
No specific criteria □
Unsure □

24. Who usually conducts the field-based exercise tests?

Physiotherapist □
Exercise physiologist □
Respiratory scientists □
Nurse □
Doctor □
Other (please list):

_____

_____

25. Please comment of the availability of personnel to conduct field-based exercise tests:

Always available □
Usually available □
Sometimes available □
Sporadically available □
Rarely available □
Not applicable □

---

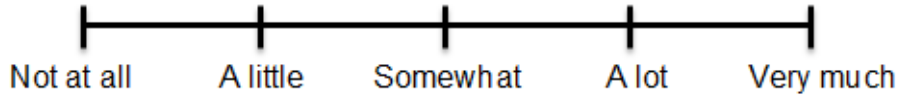
26. Please outline the main limitation to field-based exercise testing being undertaken in your centre:

Staffing availability □
Staff training □
Equipment limitations □
Equipment availability □
Not viewed as importance in our centre □
Other (please outline) □
No limitation □

27. What do you believe, if anything, would enhance field-based exercise testing in the centre? (i.e. personnel, equipment, space)

---

28. Please rate how important field-based exercise testing is to your centre using this scale:



Section 4: Strength Testing

29. Does your centre undertake peripheral strength testing? Yes/No/Unsure (if participant answers 'no', they can skip section)

30. What method is used to assess peripheral muscle strength?

1RM □
Dynamometer □
Manual muscle testing □
Unsure □

31. Muscle groups from which part of the body are assessed?

Upper limbs □
Lower limbs □
Core/trunk□
Unsure □

Section 5: Exercise Training

32. Who generally discusses physical activity and/or exercise with patients? (tick all that apply)

Physiotherapist □
Exercise physiologist □
Nurse □
Doctor □
No one □
Other (please list):

---

33. How often are physical activity and/or exercise discussed?

At every clinic appointment □
Only if the patient asks □
At annual review □
Never □
Other (please provide details):

---

34. Please comment on the availability of the outpatient exercise program, if any (tick all that apply):

No outpatient program □
Standardised outpatient exercise program (i.e. Pulmonary Rehab) □
Individually tailored exercise program □
Not applicable □ (if this response is selected, participant is permitted to skip to last question of section)

Additional comments:

---

35. Please comment on the outpatient exercise referral process (tick all that apply and feel free to provide detail in the space provided):

Patient / self-referral □
Doctor referral □
Blanket referral □
Referral from another health professional □
Unsure □

36. How does your centre triage / prioritise outpatient exercise referrals?

All patients are offered an outpatient exercise program □
Patients who are post-discharge / exacerbation are prioritised □
Patients with more severe respiratory disease are prioritised □
Other □
Unsure □
No specific system in place □

37. Please comment on how the outpatient aerobic exercise program is prescribed. Space is available to comment on which markers are used:

Using laboratory-based exercise test results

Using field-based exercise test results

Using heart rate readings

Using SpO_2 readings

Using symptom scores

Unsure

38. Please comment on how the outpatient aerobic exercise program is progressed. Space is available to comment on which markers are used:
Using laboratory-based exercise test results

Using field-based exercise test results

Using heart rate readings

Using SpO_2 readings

Using symptom scores

Unsure

39. Does your centre have a protocol regarding the level of oxygen desaturation permitted during exercise training?
Yes – test ceased at < 90% SpO_2 □
Yes – test ceased at < 85% SpO_2 □
Yes – test ceased at < 80% SpO_2 □
No specific criteria □
Unsure □

40. Please commend on the level of supervision provided in your centre:
Supervised □ (face-to-face)
Supervised □ (telehealth)
Partially supervised □
Unsupervised □
Unsure □

41. What mode of aerobic exercise is usually prescribed? You are welcome to provide additional details in the space provided:
Continuous exercise □
Interval training □
Either continuous or interval, depending on initial assessment or patient's symptoms on the day of training □
Unsure □

42. Please comment on the monitoring systems in place during outpatient exercise. You are welcome to provide details on the type of monitor (i.e. brand) in the space provided:

Oximeter □

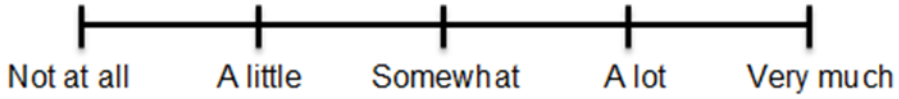
Heart rate monitor □

Symptom scores □

None □

Unsure □

43. Please rate how important exercise *training* is to your centre using this scale:



Space for any additional comments:

Thank you very much for completing this survey. Your time is greatly appreciated.

Any questions regarding the survey can be directed to the Adult CF Centre at Sir Charles Gairdner Hospital by contacting:

Abbey.Sawyer@postgrad.curtin.edu.au

References:

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Appendix 3

Cardiopulmonary exercise test protocols

Standardised protocol for ramp-based cycle ergometry test

Pre-test

1. Flow sensors, gas analysers, emergency trolley equipment calibrated as per the usual protocol prior to participant arriving.
2. Participant arrives to laboratory.
3. Participant's height and weight is collected as per the usual protocol.
4. Participant is seated in chair in the laboratory.
5. Participant is familiarised with the testing protocol (set-up, baseline measurement, incremental phase, recovery).

"You are going to complete a maximal exercise test on a bike. This will commence with a minute of rest. The difficulty of the test will be very easy at first, and will gradually increase as the test goes on. Please continue to cycle for as long as you can, until you are unable to continue. You will be asked to cycle at an RPM of 60. Each minute we will ask you about your breathlessness and leg muscle fatigue. If you are unable to maintain this for more than 30 seconds, the test will be terminated. At the end of the test, we will ask you what stopped you. Please let us know if you develop any symptoms of dizziness, chest pain, or anything else that worries you. You can do so by pointing to the area of concern. Try not to talk during the test as this will alter the results. We will be monitoring you very closely throughout the test. The doctor will stop the test if he/she is worried about the readings. Do you have any questions?"

6. Participant is asked to complete spirometry as per the standard protocol.
7. ECG leads are applied to participant as per usual protocol (i.e. shave hair as required, alcohol swab the area, brush sandpaper over the skin). Participant is asked to stand up and ECG waist strap is connected. Participant is asked to sit back down in the chair.
8. Turn on Tango (BP machine)
9. **GX > Summary** – Write down predicted HR and Work.
10. **GX > Settings Tab > Exercise Settings Tab > Default Protocol** – drop down menu:
    a. **Setting**: "x" RAMP Watt/min workload
    b. Check **Script Name = Bike Montara**
11. Place plastic and BP cuff on participant's right arm.
12. On Tango, press the ►► button to obtain a resting BP – make note of this on sheet.
13. Press the same button again to stop repeated instant BP measurement.
14. On ECG screen, press **ECG** to obtain a resting ECG.
15. Hair net and face mask is applied to participant (please record size for future testing). 'Leak' test is performed whilst participant is seated in chair.
16. Participant is asked to stand and walk to the stationary bike.
17. Once seated on the stationary bike, participant is asked to remain still. Seat height is adjusted.
18. Ear oxygen saturation probe is connected to the participant's right ear and lead is secured with tape.

19. Participant is asked to complete 1–2 revolutions to ensure seat height is correct/comfortable (refer to the previously used seat height).
20. Participant is advised that the test is about to start.

"Please remain still. We will now begin to collect 1 minute of 'resting' data. In 1 minute, we will instruct you to start pedalling. Please aim to keep the RPM at 60 throughout the test. It will be very easy, initially. The difficulty will gradually increase."

21. On Breeze program, click **Start** and on Tango press ►/■ to start 2-minute BPs.
22. Collect 1 minute of resting data.
23. Click **Exercise** and click **Yes**.

<u>During test</u>

For the purposes of the research project, please record the leg muscle fatigue and dyspnoea each minute. You don't need to fill this out on Breeze. You can use the table provided for ease.

Please provide (only) the following instructions to participant:

1. Once 1 minute of resting data has been collected, please inform the participant to start pedalling:

"Start pedalling!"

2. Each minute: please collect Borg scores and provide the following encouragement:

"You are X minutes into the test. You are doing a great job! Do as much as you can!"

- In an attempt to standardise the testing procedure, please try not to provide any other encouragement throughout the test.
- When the participant appears to be nearing the end of the test, please provide the following encouragement:

"Keep pedalling! Do as much as you can!"

3. Please continue to record recovery for 5 minutes. Patient can cycle gently during this time.
4. To stop the test, click **Recovery** and **Stop.**

<u>Post-test</u>

1. Following the 5-minute recovery, face mask is removed. Participant is asked to complete spirometry (no further spirometry required after this point).
2. Please ask participant what stopped them and write it on the sheet.
3. Participant is asked to dismount stationary bike and is seated on chair.
4. To stop Tango, press ►/■.
5. To stop ECG, select **GX > Test Tab > Stop > Yes.**
6. On ECG screen under **Quickprint** section
    a. Click **Summary**
    b. Click **12 lead ECG**
    c. Click **Save Report**
    d. Click **Exit**
7. ECG leads and stickers are removed.
8. Participant is informed that the test has finished.

Standardised protocol for constant work rate cycle ergometry test

Pre-test

1. Flow sensors, gas analysers, medical emergency trolley equipment calibrated as per the usual protocol prior to participant arriving.
2. Participant arrives to laboratory.
3. Participant's height and weight is collected as per the usual protocol.
4. Participant is seated in chair in the laboratory and asked if they have any question or comments about the previous test. They are then given the following instructions:

"You are going to complete an endurance exercise test on a bike. This will commence with a minute of rest. The difficulty of the test will then increase to 80% of what you achieved in the previous test. Please continue to cycle for as long as you can, until you are unable to continue. You will be asked to cycle at an RPM of 60. Each minute we will ask you about your breathlessness and leg muscle fatigue. If you are unable to maintain this for more than 30 seconds, the test will be terminated. At the end of the test, we will ask you what stopped you. Please let us know if you develop any symptoms of dizziness, chest pain, or anything else that worries you. You can do so by pointing to the area of concern. Try not to talk during the test as this will alter the results. We will be monitoring you very closely throughout the test. The doctor will stop the test if he/she is worried about the readings. Do you have any questions?"

5. Participant is asked to complete spirometry as per the standard protocol.
6. ECG leads are applied to participant as per usual protocol (i.e. shave hair as required, alcohol swab the area, brush sandpaper over the skin). Participant is asked to stand up and ECG waist strap is connected. Participant is asked to sit back down in the chair.
7. Turn on Tango (BP machine).
8. **GX > Settings Tab > Exercise Settings Tab > Default Protocol** – drop down menu:
    a. **Setting**: 'ZCFIIT (participant number will be here) Constant'
    b. Check **Script Name = Bike Montara**
9. Place plastic and BP cuff on participant's right arm.
10. On Tango, press the ►► button to obtain a resting BP – make note of this on sheet.
11. Press the same button again to stop repeated instant BP measurement.
12. On ECG screen, press **ECG** to obtain a resting ECG.
13. Hair net and face mask is applied to participant (please record size for future testing). 'Leak' test is performed whilst participant is seated in chair.
14. Participant is asked to stand and walk to the stationary bike.
15. Once seated on the stationary bike, participant is asked to remain still. Seat height is adjusted.
16. Ear oxygen saturation probe is connected to the participant's right ear and lead is secured with tape.
17. Participant is asked to complete 1–2 revolutions to ensure seat height is correct/comfortable (refer to the previously used seat height).
18. Participant is advised that the test is about to start.

"Please remain still. We will now begin to collect 1 minute of 'resting' data. In 1 minute, we will instruct you to start pedalling. Please aim to keep the RPM at 60 throughout the test. After the initial unloaded period, the difficulty will increase to 80% of what you achieved during the previous test."

19. On Breeze program, click **Start** and on Tango press ►/■ to start 2-minute BPs.

20. Collect 1 minute of resting data.
21. Click **Exercise** and click **Yes**.

During test

For the purposes of the research project, please record the leg muscle fatigue and dyspnoea each minute. You don't need to fill this out on Breeze. You can use the table provided for ease.

Please provide (only) the following instructions to participant:

1. Once 1 minute of resting data has been collected, please inform the participant to start pedalling:

   "Start pedalling!"

2. Each minute: please collect Borg scores and provide the following encouragement:

"You are X minutes into the test. You are doing a great job! Do as much as you can!"

- In an attempt to standardise the testing procedure, please try not to provide any other encouragement throughout the test.
- When the participant appears to be nearing the end of the test, please provide the following encouragement:

  "Keep pedalling! Do as much as you can!"

3. Please continue to record recovery for 5 minutes. Patient can cycle gently during this time.
4. To stop the test, click **Recovery** and **Stop.**

Post-test

1. Following the 5-minute recovery, face mask is removed. Participant is asked to complete spirometry (no further spirometry required after this point).
2. Please ask participant what stopped them and write it on the sheet.
3. Participant is asked to dismount stationary bike and is seated on chair.
4. To stop Tango, press ►/■.
5. To stop ECG, select **GX > Test Tab > Stop > Yes.**
6. On ECG screen under **Quickprint** section
   a. Click **Summary**
   b. Click **12 lead ECG**
   c. Click **Save Report**
   d. Click **Exit**
7. ECG leads and stickers are removed.
8. Participant is informed that the test has finished.

Appendix 4

Baseline observation carried forward analysis

Ramp-based cycle ergometry test

Between-group differences

Compared with the magnitude of change in peak work rate (W_{peak}) (Watts; W) seen in the control group, greater change (increase) in W_{peak} was seen in the experimental group (between-group difference p = 0.009). This change was also seen when analysed according to W_{peak} % predicted (between-group difference p = 0.006) (Table A4.1).

Within-group differences

In the experimental group, compared with baseline measures, improvement was noted in W_{peak} (median difference 6 W [95% CI 0 to 10]. In the experimental group, compared with baseline measures, improvement was noted in anaerobic threshold as a percentage of predicted VO_{2peak} (3% [95% CI 0 to 12]. No other within-group changes were demonstrated in the experimental or control group.

Table A4.1 Between-group differences in maximal exercise capacity using baseline observation carried forward analysis

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
VO_{2peak} ($L \cdot min^{-1}$)	2.17 [1.70, 2.79]	2.17 [1.70, 3.04]	1.94 [1.60, 2.31]	1.94 [1.53, 2.31]	p = 0.52
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	30.01 [22.60, 39.75]	30.01 [22.60, 42.10]	25.36 [21.27, 30.85]	25.36 [20.18, 30.23]	p = 0.29
VO_{2peak} (% predicted)	83 [75, 105]	90 [75, 114]	66 [62, 85]	66 [58, 85]	p = 0.18
VCO_{2peak} ($L \cdot min^{-1}$)	2.64 [2.12, 3.52]	2.64 [2.02, 3.40]	2.39 [1.95, 2.81]	2.20 [1.95, 2.62]	p = 0.43
W_{peak} (Watts)	176 [122, 241]	176 [132, 253]	183 [120, 207]	183 [120, 203]	**p = 0.009****
W_{peak} (% predicted)	89 [78, 138]	90 [78, 148]	85 [70, 86]	82 [68, 85]	**p = 0.006****
End-test breathlessness	7 [5, 8]	7 [5, 9]	8 [4, 8]	6 [4, 8]	p = 0.60
End-test leg fatigue	9 [8, 10]	9 [7, 10]	9 [7, 9]	7 [5, 9]	p = 0.29
Nadir SpO_2 (%)	93 [92, 94]	94 [91, 95]	93 [91, 94]	94 [89, 97]	p = 0.79
HR_{max} (bpm)	168 [152, 177]	172 [158, 173]	161 [159, 170]	159 [159, 170]	p = 0.21
HR_{max} (% predicted)	86 [81, 95]	86 [84, 92]	89 [84, 93]	88 [83, 93]	p = 0.23
End-test RR ($breaths \cdot min^{-1}$)	44 [40, 51]	48 [42, 51]	33 [31, 46]	33 [30, 46]	p = 0.63
O_2 pulse	12 [11, 16]	12 [11, 21]	11 [8, 15]	11 [8, 15]	p = 0.81
AT (% VO_{2peak})	42 [41, 57]	46 [42, 63]	32 [27, 45]	41 [29, 47]	p = 0.35
V_{Epeak} ($L \cdot min^{-1}$)	72.88 [60.58, 107.00]	72.88 [60.58, 108.00]	61.37 [58.33, 71.10]	60.66 [56.73, 67.00]	p = 0.08
VO_2 / work slope ($mL \cdot min^{-1}$ W^{-1})	10.54 [9.00, 10.68]	10.10 [9.00, 10.68]	9.70 [8.11, 9.80]	9.72 [8.30, 9.80]	p = 0.74

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p values). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: AT: anaerobic threshold, bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, O_2 pulse: oxygen pulse, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, VCO_{2peak}: peak rate of carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake, W_{peak}: peak work rate. End-test symptoms measured using the Borg scale (0 to 10).

Constant work rate cycle ergometry test

Between-group differences

Compared with the magnitude of change in T_{lim} (seconds) seen in the control group, greater change was seen in the experimental group (between-group difference p = 0.02). There were no other between-group changes in other measures of exercise capacity collected during the constant work rate cycle ergometry test following the intervention period (Table A4.2).

Within-group differences

In the experimental group, compared with baseline measures, improvement was noted in T_{lim} of 260 seconds. The 95% CI for this measure crossed zero (−2 to 381). In the control group, compared with baseline measures, deterioration was noted in respiratory rate of 3 breaths per minute (95% CI 0 to 9). No other within-group changes were demonstrated in the experimental or control group.

Table A4.2 Between-group differences in endurance exercise capacity using baseline observation carried forward analysis

Variable	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
T_{lim} (seconds)	254 [222, 360]	502 [254, 620]	248 [210, 306]	230 [220, 306]	**p = 0.020****
VO_{2peak} ($L \cdot min^{-1}$)	2.05 [1.60, 2.90]	2.05 [1.69, 3.98]	1.72 [1.43, 3.36]	1.72 [1.48, 2.22]	p = 0.18
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	28.34 [21.55, 40.27]	28.33 [22.53, 40.68]	23.46 [18.25, 31.01]	23.47 [18.25, 29.64]	p = 0.18
VO_{2peak} (% predicted)	86 [67, 105]	88 [71, 112]	67 [51, 73]	62 [51, 73]	p = 0.20
VCO_{2peak} ($L \cdot min^{-1}$)	2.74 [1.89, 3.16]	2.74 [1.91, 2.90]	2.35 [1.61, 2.85]	2.17 [1.61, 2.67]	p = 0.90
End-test Breathlessness	7 [5, 8]	8 [5, 9]	7 [5, 8]	7 [4, 9]	p = 0.33
End-test Leg muscle fatigue	9 [7,10]	9 [5, 10]	7 [4, 9]	5 [4, 9]	p = 0.94
Nadir SpO_2 (%)	93 [89, 95]	93 [89, 95]	95 [91, 97]	94 [91, 96]	p = 0.12
HR_{max} (bpm)	167 [148, 171]	166 [158, 171]	156 [146, 167]	156 [154, 162]	p = 0.25
End-test RR ($breaths \cdot min^{-1}$)	44 [43, 49]	46 [45, 49]	30 [26, 39]	38 [28, 40]	p = 0.19
V_{Epeak} ($L \cdot min^{-1}$)	72.07 [55.91, 104.00]	72.40 [64.00, 107.97]	57.06 [44.84, 68.60]	57.36 [44.84, 67.00]	p = 0.80

Data are presented as median [IQR]. Between-group data were analysed using rank-sum tests (reported as p values). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: bpm: beats per minute, HR_{max}: maximal heart rate, IQR: interquartile range, RR: respiratory rate, SpO_2: peripheral capillary oxygen saturation, T_{lim}: time to symptom limitation, VCO_{2peak}: peak rate of carbon dioxide production, V_{Epeak}: peak minute ventilation, VO_{2peak}: peak rate of oxygen uptake. End-test symptoms measured using the Borg scale (0 to 10).

Appendix 5

Respiratory function

Table A5.1 Respiratory function of participants in the randomised controlled trial at baseline

	Experimental group (n = 7)		Control group (n = 7)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Between-group difference**
FEV_1 (L)	2.2 [1.9, 3.4]	2.2 [1.9, 3.4]	1.8 [1.7, 3.6]	1.8 [1.5, 3.5]	p = 1.00
FEV_1 (% predicted)	66 [45, 83]	66 [53, 81]	57 [39, 80]	58 [37, 78]	p = 0.95
FVC (L)	3.3 [3.0, 5.6]	3.2 [2.5, 5.7]	3.6 [3.1, 5.2]	3.3 [3.1, 5.0]	p = 1.00
FVC (% predicted)	88 [62, 100]	83 [60, 98]	79 [64, 92]	68 [59, 92]	p = 0.18
FEV_1/FVC	67 [61, 72]	70 [64, 75]	60 [54, 69]	69 [51, 77]	p = 0.48

Data are presented as median [IQR] unless otherwise stated. Between-group data are analysed using rank-sum tests (reported as p value). **: between-group difference in the magnitude of change from baseline to follow-up. Abbreviations: FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, IQR: interquartile range. Global Lung Index Initiative lung function reference values used [386].

Note: The FEV_1/FVC ratio increased from 60 to 69% in the control group following the intervention period. This change appears to reflect a reduction in the median FVC % predicted in both groups.

Appendix 6

BCT Taxonomy (v1) [82]

1. Goals and planning
1.1. Goal setting (behaviour)
1.2. Problem solving
1.3. Goal setting (outcome)
1.4. Action planning
1.5. Review behavior goal(s)
1.6. Discrepancy between current behaviour and goal
1.7. Review outcome goal(s)
1.8. Behavioral contract
1.9. Commitment
2. Feedback and monitoring
2.1. Monitoring of behaviour by others without feedback
2.2. Feedback on behaviour
2.3. Self-monitoring of behaviour
2.4. Self-monitoring of outcome(s) of behaviour
2.5. Monitoring of outcome(s) of behavior without feedback
2.6. Biofeedback
2.7. Feedback on outcome(s) of behavior
3. Social support
3.1. Social support (unspecified)
3.2. Social support (practical)
3.3. Social support (emotional)
4. Shaping knowledge
4.1. Instruction on how to perform the behavior
4.2. Information about antecedents
4.3. Re-attribution
4.4. Behavioral experiments
5. Natural consequences
5.1. Information about health consequences
5.2. Salience of consequences
5.3. Information about social and environmental consequences
5.4. Monitoring of emotional consequences
5.5. Anticipated regret
5.6. Information about emotional consequences
6. Comparison of behaviour
6.1. Demonstration of the behavior
6.2. Social comparison
6.3. Information about others' approval
7. Associations
7.1. Prompts/cues
7.2. Cue signalling reward
7.3. Reduce prompts/cues
7.4. Remove access to the reward
7.5. Remove aversive stimulus
7.6. Satiation
7.7. Exposure
7.8. Associative learning
8. Repetition and substitution
8.1. Behavioral practice/rehearsal
8.2. Behavior substitution
8.3. Habit formation
8.4. Habit reversal
8.5. Overcorrection
8.6. Generalisation of target behavior
8.7. Graded tasks
9. Comparison of outcomes
9.1. Credible source
9.2. Pros and cons
9.3. Comparative imagining of future outcomes
10. Reward and threat
10.1. Material incentive (behavior)
10.2. Material reward (behavior)
10.3. Non-specific reward
10.4. Social reward
10.5. Social incentive
10.6. Non-specific incentive
10.7. Self-incentive
10.8. Incentive (outcome)
10.9. Self-reward
10.10. Reward (outcome)
10.11. Future punishment
11. Regulation
11.1. Pharmacological support
11.2. Reduce negative emotions
11.3. Conserving mental resources
11.4. Paradoxical instructions
12. Antecedents
12.1. Restructuring the physical environment
12.2. Restructuring the social environment
12.3. Avoidance/reducing exposure to cues for the behavior
12.4. Distraction
12.5. Adding objects to the environment
12.6. Body changes
13. Identity
13.1. Identification of self as role model
13.2. Framing/reframing
13.3. Incompatible beliefs
13.4. Valued self-identify
13.5. Identity associated with changed behavior
14. Scheduled consequences
14.1. Behavior cost

14.2. Punishment
14.3. Remove reward
14.4. Reward approximation
14.5. Rewarding completion
14.6. Situation-specific reward
14.7. Reward incompatible behavior
14.8. Reward alternative behavior
14.9. Reduce reward frequency
14.10. Remove punishment
15. Self-belief
15.1. Verbal persuasion about capability
15.2. Mental rehearsal of successful performance
15.3. Focus on past success
15.4. Self-talk
16. Covert learning
16.1. Imaginary punishment
16.2. Imaginary reward
16.3. Vicarious consequences

Behaviour change mechanisms of action

Mechanism label	Mechanism definition
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/Professional Role and Identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Beliefs about Capabilities	Beliefs about one's ability to successfully carry out a behaviour
Optimism	Confidence that things will happen for the best or that desired goals will be attained
Beliefs about Consequences	Beliefs about the consequences of a behaviour (i.e. perceptions about what will be achieved and/or lost by undertaking a behaviour, as well as the probability that a behaviour will lead to a specific outcome)
Reinforcement	Processes by which the frequency or probability of a response is increased through a dependent relationship or contingency with a stimulus or circumstance
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, Attention, and Decision Processes	Ability to retain information, focus on aspects of the environment, and choose between two or more alternatives
Environmental Context and Resources	Aspects of a person's situation or environment that discourage or encourage the behaviour
Social Influences	Those interpersonal processes that can cause oneself to change one's thoughts, feelings or behaviours
Emotion	A complex reaction pattern involving experiential, behavioural and physiological elements
Behavioural Regulation	Behavioural, cognitive and/or emotional skills for managing or changing behaviour

Norms	The attitudes held and behaviours exhibited by other people within a social group
Subjective Norms	One's perceptions of what most other people within a social group believe and do
Attitude towards the Behaviour	The general evaluations of the behaviour on a scale ranging from negative to positive
Motivation	Processes relating to the impetus that gives purpose or direction to behaviour and operates at a conscious or unconscious level
Self-image	One's conception and evaluation of oneself, including psychological and physical characteristics, qualities and skills
Needs	Deficit of something required for survival, well-being or personal fulfilment
Values	Moral, social or aesthetic principles accepted by an individual or society as a guide to what is good, desirable or important
Feedback Processes	Processes through which current behaviour is compared against a particular standard
Social Learning/Imitation	A process by which thoughts, feelings, and motivational states observed in others are internalised and replicated without the need for conscious awareness
Behavioural Cueing	Processes by which behaviour is triggered from either the external environment, the performance of another behaviour, or from ideas appearing in consciousness
General Attitudes/Beliefs	Evaluations of an object, person, group, issue or concept on a scale ranging from negative to positive
Perceived Susceptibility/Vulnerability	Perceptions of the likelihood that one is vulnerable to a threat

Note: Written permission was provided from the senior author to reproduce this table.

Appendix 7

Author contribution statements and permissions

Sawyer A, Cavalheri V, Jenkins S, Wood J, Singh B, Hill K. Endurance cycle ergometry tests performed at a sub-maximal work rate elicit peak physiological and symptom responses in adults with cystic fibrosis. Submitted for publication in February 2020.

Conception and Design	Acquisition of Data and Method	Data Conditioning/ Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Final Approval	Total % contribution
Co-Author 1: Abbey Sawyer	✓	✓	✓	✓	✓	30%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 2: Vinicius Cavalheri	✓	✓	✓	✓	✓	20%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 3: Sue Jenkins	✓	✓	✓	✓	✓	15%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 4: Jamie Wood	✓			✓	✓	5%
Co-Author 4 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 5: Bhajan Singh	✓				✓	5%
Co-Author 5 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 6: Kylie Hill	✓	✓	✓	✓	✓	25%
Co-Author 6 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Total %						**100%**

Sawyer A, Cavalheri V, Hill K. Effects of high intensity interval training on exercise capacity in people with chronic pulmonary disease: a narrative review. BMC Sports Sci Med Rehabil. 2020;30(12):22. doi:10.1186/s13102-020-00167-y.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Abbey Sawyer	✓	✓	✓	✓	✓	45%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 2: Vinicius Cavalheri	✓	✓	✓	✓	✓	25%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 3: Kylie Hill	✓	✓	✓	✓	✓	30%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Total %						**100%**

Sawyer A, Cavalheri V, Wood J, Hill K. Exercise testing and exercise training within cystic fibrosis centres across Australia and New Zealand: what is considered important and what is current practice? Intern Med J. 2019; [Epub ahead of print]. doi:10.1111/imj.14443.

Conception and Design	Acquisition of Data and Method	Data Conditioning/ Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Final Approval	Total % contribution
Co-Author 1: Abbey Sawyer	✓	✓	✓	✓	✓	40%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 2: Vinicius Cavalheri	✓	✓	✓	✓	✓	20%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 3: Jamie Wood	✓			✓	✓	15%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 4: Kylie Hill	✓	✓	✓	✓	✓	25%
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Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Singh B, Hill K. Effects of high intensity interval training on exercise capacity in people with cystic fibrosis: study protocol for a randomised controlled trial. BMC Sports Sci Med Rehabil. 2018;6(10):19. doi:10.1186/s13102-018-0108-2.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Abbey Sawyer	✓	✓	✓	✓	✓	30%
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Co-Author 2: Vinicius Cavalheri	✓	✓	✓	✓	✓	20%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 3: Sue Jenkins	✓	✓	✓	✓	✓	10%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 4: Jamie Wood	✓			✓	✓	5%
Co-Author 4 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 5: Nola Cecins	✓				✓	5%
Co-Author 5 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 6: Bhajan Singh	✓	✓		✓	✓	10%
Co-Author 6 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 7: Kylie Hill	✓	✓	✓	✓	✓	20%
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Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Abbey Sawyer	✓	✓	✓	✓	✓	30%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 2: Hayley Lewthwaite	✓	✓	✓		✓	20%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 3: Daniel Gucciardi	✓	✓		✓	✓	15%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 4: Kylie Hill	✓	✓	✓	✓	✓	10%
Co-Author 4 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 5: Sue Jenkins	✓			✓	✓	5%
Co-Author 5 Acknowledgment: I acknowledge that these represent my contribution to the above research output						
Co-Author 6: Vinicius Cavalheri	✓	✓	✓	✓	✓	20%
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