School of Public Health

Associations between residential indoor air pollutants with sub-clinical measures of cardiometabolic risk

Suzanne Erica Gilbey

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ORCID ID: 0000-0003-3893-299X

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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 acknowledgment has been made.

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

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number HRE2016-0308.

Suzanne Erica Gilbey

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Date

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ABSTRACT

A growing body of epidemiological and clinical evidence implicates exposure to various ambient air pollutants as an emerging risk factor for cardiometabolic disease. However, few studies have investigated how indoor residential environments, where individuals spend most of their daily time, impact functional pre-clinical markers of cardiovascular and metabolic health.

This cross-sectional study aimed to investigate associations between exposure to selected domestic indoor air pollutants with a range of biomarkers related to sub-clinical cardiometabolic risk. This research is unique as it is believed to be the first study to examine the relationship between residential indoor air quality (IAQ) with such a comprehensive range of risk markers connected with cardiometabolic health.

Data was collected from a cohort of 111 apparently healthy, non-smoking adults (65% female) living in non-smoking households. Participants were aged between 35 and 69 years and were recruited from the Perth metropolitan area in Western Australia.

Participants were ineligible to join the study if they met any of the following exclusion criteria:

- A history of cardiovascular events or medical diagnosis of cardiovascular disease;
- Medically diagnosed diabetes;
- Use of anti-hypertensive or lipid modifying medications and/or;
- Lack of written consent.

Data collection for each participant involved a two-stage process and included:

- *Home stage*: Concurrent in-home measurement of 24-hour domestic indoor and outdoor air quality along with ambulatory blood pressure and hemodynamic indices. Participants also completed questionnaires related to their health and domestic environment and completed a 24-hour time/activity diary during the air quality/blood pressure monitoring period.

- *Clinic stage*: A fasting clinic-based health assessment, where along with the taking of a health history, blood and urine samples were collected to ascertain the participant's lipid, glucose homeostasis and renal function profiles. A pulse wave analysis was carried out to establish carotid-femoral pulse wave velocity. Baseline anthropometric measurements such as height, weight and waist and hip circumference measurements were recorded.

In this study, significant positive associations were demonstrated per interquartile (IQR) increase in total volatile organic compound (TVOC) concentration with 24-hour (AIx: 1.00%; 95% CI: 0.25, 1.87; $p = 0.011$; AIx_{75}: 0.87%; 95% CI: 0.12, 1.74; $p = 0.028$), daytime (AIx: 1.25%; 95% CI: 0.37, 2.12; $p = 0.009$; AIx_{75}: 1.00%; 95% CI: 0.12, 1.87; $p = 0.023$) and nighttime (AIx: 0.87%; 95% CI: 0.12, 1.74; $p = 0.033$; AIx_{75}: 0.87%; 95% CI: 0.00, 1.74; $p = 0.064$) augmentation index (AIx; %) and AIx adjusted for heart rate (AIx_{75}; %). Interquartile increases in formaldehyde (HCHO) levels was associated with 24-hour AIx (2.37%; 95% CI: 0.12, 4.61; $p = 0.039$) and AIx_{75} (2.29%; 95% CI: 0.01, 4.56; $p = 0.049$) and daytime AIx_{75} (2.51%; 95% CI: 0.06, 4.96; $p = 0.045$). Small, significant, sub-optimal associations were demonstrated between an IQR increase in carbon dioxide (CO_2) with lipid biomarkers including high density lipoprotein (HDL) cholesterol (-0.24 mmol/L; 95% CI: -0.37, -0.12; $p < 0.001$) and total cholesterol/HDL (TC/HDL; 0.28; 95% CI: 0.01, 0.54; $p = 0.040$). A similar association was shown between CO_2 with glycated haemoglobin (HbA1c; 0.08%; 95% CI: 0.00, 0.17; $p = 0.041$).

Significant inverse associations were observed between an IQR increase in nitrogen dioxide (NO_2) with central systolic blood pressure (SBP) measures (24-hour: -2.40 mmHg; 95% CI: -4.74, -0.05; $p = 0.045$; daytime SBP: -2.10 mmHg; 95% CI: - 4.02, -0.17; $p = 0.033$) and 24-hour (-1.07 mmHg; 95% CI: -2.12, -0.02; $p = 0.046$) and nighttime pulse pressure (PP; -1.28 mmHg; 95% CI: -2.49, -0.07; $p = 0.038$). Whilst support for these findings is provided by recently published literature, no explanation for this unexpected outcome is offered.

No significant relationships were found between larger sized particulate matter (PM) (total PM, PM_{10}, PM_4, $PM_{2.5}$ or PM_1) with any measured cardiometabolic risk factor, although significant associations were observed between an IQR increase in ultrafine particle (UFP) numbers with measures of aortic arterial stiffness including 24-hour AIx

(5.38%; 95% CI: 0.19, 10.56; p =0.043), nighttime AIx (6.10%; 95% CI: 1.45, 10.78; p = 0.012), 24-hour AIx_{75} (6.14%; 95% CI: 1.33, 10.96; p = 0.014), daytime AIx_{75} (5.84%; 95% CI: 0.27, 11.42; p = 0.041), nighttime AIx_{75} (7.21%; 95% CI: 2.46, 11.97; p = 0.004), 24-hour PP (-2.28 mmHg; 95% CI: -4.53, -0.01; p =0.049) and daytime PP (-2.64; 95% CI: -4.89, -0.37; p =0.024).

In this cohort of healthy middle-aged adults living in Perth, Western Australia, exposure to typically encountered concentrations of several indoor residential air pollutants was significantly and adversely associated with a range of biomarkers related to cardiometabolic risk. These findings are important as not only have they contributed to the currently limited body of knowledge that exists regarding the relationship between domestic IAQ and sub-clinical outcomes related to cardiometabolic risk, but they have been established at relatively low concentrations of exposure. Whilst IAQ guidelines exist for some pollutants in Canada, Japan and a number of European countries, no specific standards or guidelines exist in Australia. The findings of this study add further weight to the common view that low concentration exposure to some pollutants below current environmental and ambient air quality guidelines, are capable of instigating unfavourable effects on functional intermediate cardiometabolic risk markers. Further studies however, are recommended to corroborate these findings.

Although some of the observed effects are small, they are noted to pose some risk for apparently healthy people. These results are consistent with growing evidence from ambient pollution studies, and in context with the broader literature and if supported by further research outcomes, may have important implications regarding the impact of residential air pollution on cardiometabolic health, particularly in vulnerable populations. These outcomes provide additional support for the application of appropriate public health policies and/or guidelines on IAQ that aim to optimally protect the cardiometabolic health of all.

This thesis is dedicated to the memory of my Dad.

"Great things happen to those who don't stop believing, trying, learning, and being grateful"

Roy T Bennett, The Light in the Heart

ACKNOWLEDGEMENT

On a daily basis we are presented with opportunities; some we choose to embrace and learn from, others we decide not to pursue. Undertaking this research and writing this thesis has been an extraordinary opportunity; one for which I am extremely grateful and so glad I pursued. I am also extremely fortunate that my enlightenment and comprehension of the level of commitment, effort, patience and passion required to undertake this journey joined me at the point of 'no-turning-back' – for that I am extremely grateful!

However, my PhD journey would never have been possible without such a generous, patient and professional supervisory team – Krassi, Chris, Rachel, Mario and Yun. I cannot thank you enough for your unwavering belief in me and my project, and for your untiring support, wisdom and commitment to mentoring me from a tentative idea to PhD submission.

To the CCRE girls; Jacquita, Ally and Annie. Thank you for helping me to see humour in non-humorous situations (so many of them!!) and keeping the clinical side of things running smoothly. Thank you to Edwin and Thaila in the SoPH labs for tracking down my MIA air monitoring equipment to international locations where apparently, they are required to go for an extended break (!) and calibration. And Thaila, it looks like your dream might actually come true!

To all the participants who allowed me into their homes, endured a lengthy fast, allowed me to prick holes in them and good-naturedly tolerated being woken up every 30 minutes as blood pressure cuffs went up and down, day and night! Thank you!

To my Dad and Mum who never faltered in their support and belief that this journey would be completed, I am just so appreciative. Particularly special thanks to my beautiful Dad; a fine and esteemed scholar himself, who offered gentle advice and encouraged me to continue on to achieve my dream despite facing terminal illness. His dream was to see me walk off stage holding my PhD. Dad will not see me at the Graduation Ceremony he so dearly wanted to attend, however I know he will proudly be there in spirit.

And lastly, to my ever-patient partner Simon, and my incredible and amazingly tolerant children, Harry, Austin and Amy. None of you wavered in your support and encouragement despite a frequently empty fridge, reheated/bought/very late/non-existent dinners, missed parent-teacher evenings and piled-up laundry. Thank you from the bottom of my heart for always believing in me, especially when I wasn't even sure myself!

Finally, as one last reflection, this PhD journey was long, and at times the finishing line seemed insurmountable. I came across this email I wrote to one of my Supervisors which somehow perfectly sums up the last 5 years….

"I have now finally finished data collection and am sorting out (so much) data, frantically writing my thesis and putting together drafts of a number of manuscripts – you should start to see those coming through shortly. I love this exciting phase now though, where I see the fruit of all my thousands of kilometres (9000km to be exact-ish) travelled, and hours and hours of medical assessments when a) people forget to turn up despite confirming; b) they haven't fasted; c) equipment has broken down so the whole project stalls or; d) everything goes to schedule and the air monitoring and the medical is completed just as planned!! I learnt very quickly to very sincerely be able to say 'that's OK, we can reschedule' through gritted teeth as I saw my time-lines getting further and further away from me, and the prospect of me having my own cardiovascular event occurring, a real thing!!! Retrospect is a great thing though, because it now doesn't seem that bad and those incredibly frustrating moments have turned into small blips when I am now starting to see results! Exciting times!"

19 June 2018

I am just so thankful to be finished.

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PUBLICATIONS ARISING FROM THIS WORK

Although this thesis is presented for examination in the format of a traditional dissertation, the following publications have been generated from this research.

I contributed to conceptualising the scope and design of the research, the aim and the objectives, conducted data collection, statistical design and analysis, interpretation of the findings and prepared drafts of the manuscripts.

Gilbey, S. E., Reid, C. M., Huxley, R. R., Soares, M. J., Zhao, Y., & Rumchev, K. (2019). Associations Between Sub-Clinical Markers of Cardiometabolic Risk and Exposure to Residential Indoor Air Pollutants in Healthy Adults in Perth, Western Australia: A Study Protocol. *International Journal of Environmental Research and Public Health, 16*(19), ***In part – Chapter 3 of this thesis.***

Gilbey, S. E., Reid, C. M., Huxley, R. R., Soares, M. J., Zhao, Y., & Rumchev, K. Domestic Exposure to Indoor Volatile Organic Compounds and their Relationship with Measures of Central Arterial Stiffness. This manuscript has been accepted for presentation at the Joint Meeting of the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH), Glasgow, UK. April 11 – 14, 2021 (postponed from June 2020). ***In part – Chapter 4 of this thesis.***

Gilbey, S. E., Reid, C. M., Huxley, R. R., Soares, M. J., Zhao, Y., & Rumchev, K. The Effect of Dwelling Characteristics and Occupant Activities on Indoor Particle and Pollutant Concentrations in Residential Homes in Perth, Western Australia. (In draft). ***In part – Chapter 4 of this thesis.***

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LIST OF ABBREVIATIONS

ABP	ambulatory blood pressure
ABPM	Ambulatory Blood Pressure Monitor
A/C	air conditioning
ACR	Albumin/Creatinine Ratio
AHF	Australian Heart Foundation
AIx	augmentation index
AIx_{75}	augmentation index normalized to a heart rate of 75 beats per minute
AP	augmented pressure
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
c or (c)	central; describes a measurement from the central circulatory system
cfPWV	carotid-femoral pulse wave velocity
CI	confidence interval.
CO	carbon monoxide.
CO_2	carbon dioxide.
CKD	chronic kidney disease
DBP	diastolic blood pressure
CM	cardiometabolic
CMD	cardiometabolic disease

CV	cardiovascular
CVD	cardiovascular disease.
d_a	equivalent aerodynamic diameter
DBP	diastolic blood pressure
DEARS	Detroit Exposure and Aerosol Research study
eGFR	estimated glomerular filtration rate
GBD	Global Burden of Disease
GEO	flued/unflued gas, electric or oil heating
GLM	general linear model
HbA1c	glycated haemoglobin.
HCHO	formaldehyde.
HDL	high density lipoprotein cholesterol
HR	heart rate.
IAQ	indoor air quality.
IARC	International Agency for Research on Cancer.
IQR	interquartile range
LDL	low density lipoprotein cholesterol
MAP	mean arterial pressure
MESA-Air	Multi-Ethnic Study of Atherosclerosis
Meta-AIR	Metabolic and Asthma Incidence Research
MD	mean difference
MI	myocardial infarction.
NEPM-AAQ	National Environmental Protection Measure for ambient air quality.

NHANES III	The Third National Health and Nutrition Examination Survey
NHMRC	National Health and Medical Research Council
NO_2	nitrogen dioxide.
NO_x	oxides of nitrogen.
NSHAP	National Social Life, Health, and Aging Project.
PM	particulate matter.
p or (p)	peripheral
PM_{10}	particulate matter with an d_a of smaller than 10 microns.
PM_4	particulate matter with an d_a of smaller than 4 microns.
$PM_{2.5}$	particulate matter with an d_a of smaller than 2.5 microns.
PM_1	particulate matter with an d_a of 1 micron or less.
PP	pulse pressure
PVC	polyvinyl chloride.
PWA	pulse wave analysis
PWV	pulse wave velocity
RACGP	Royal Australian College of General Practitioners
RC A/C	reverse cycle air conditioning
REGICOR	Registre Gironi del Cor cohort study
RH	relative humidity
SBP	systolic blood pressure
SD	standard deviation.
SES	socio-economic status
SO_2	sulphur dioxide

SWAN	US Study of Women's Health Across the Nation
T2DM	type 2 diabetes mellitus.
TC	total cholesterol
TC/HDL	total cholesterol/high density lipoprotein ratio
TG	triglycerides
TPM	total particulate matter
TVOC	total volatile organic compounds
TWSHHH	Taiwanese Survey on Prevalence of Hyperglycaemia, Hyperlipidaemia, and Hypertension
UFP	ultrafine particulates with an aerodynamic diameter of 0.1 μm or less.
VOC	volatile organic compounds.
WHO	World Health Organisation

UNITS OF MEASUREMENT AND CONCENTRATION

° C	degrees celcius
mmHg	millimetres of mercury
mmol/L	millimole per litre
mg/L	milligrams per litre
mg/mmol	milligrams per millimole
ppm	parts per million by volume (1 000 000)
ppb	parts per billion by volume (1 000 000 000)
particles/cm^3	particles per cubic centimetre
µg/m^3	microgram per cubic metre (g x 10^{-6})
µm	microns

CHAPTER ONE – INTRODUCTION

Chapter one provides a general background to modern-day air pollution exposure research and its origins as a risk factor for adverse human health outcomes. It also provides a perspective on air pollution exposure and its impact on health systems. Finally, this chapter identifies gaps in our current state of knowledge and outlines the study aim, hypothesis and objectives.

1.1 Background

Extreme air pollution events in London and Europe during the mid 1900s are generally considered to be the catalyst for the study of air pollution epidemiology and associated adverse health outcomes (Bell, Davis, & Fletcher, 2004; Hooper & Kaufman, 2018; Seinfeld, 2004). Modern research into air pollution induced health effects began after isolated episodes such as Belgium's 1930 Meuse Valley fog, and the 1952 London Smog which saw exceptionally high concentrations of pollution when industrialization and urbanization met with particularly stagnant meteorological conditions (Hooper & Kaufman, 2018). Both episodes resulted in significantly higher and persistent mortality rates above the normal (Bell et al., 2004; Claeys, Rajagopalan, Nawrot, & Brook, 2017; Davis, Bell, & Fletcher, 2002; Hooper & Kaufman, 2018).

During the London Smog, respiratory causes contributed to the greatest increase in mortality, however the majority of excess deaths were from cardiovascular complications (Claeys et al., 2017; Davis et al., 2002; Logan, 1953). This episode was deemed to be the stimulus, and a direct incentive to pass the Clean Air Act in 1956 which saw the introduction of measures to reduce air pollution (F. J. Kelly & Fussell, 2015). This episode is also believed to have contributed to legislative changes by the late 1970's, which have led to greatly reduced and continuous declines in concentrations of air pollutants in high-income countries (Hamanaka & Mutlu, 2018; Schulz et al., 2019; Wilson, Kingham, Pearce, & Sturman, 2005).

Since these and several more recent air pollution episodes, extensive evidence has been provided by public health researchers supporting that acutely elevated exposures do not cause only acutely evident public health effects, but that these exposures also contribute to chronic health problems (Pope., 2000).

1.1.1 A perspective on air pollution

Air pollution is considered the largest environmental cause of disease and premature death in the world today with data from the Global Burden of Disease (GBD) study (Forouzanfar et al., 2016) estimating that pollution-mediated disease contributed to 9 million premature deaths in 2015 – or 16% of total global mortality (Forouzanfar et al., 2016; Landrigan, Fuller, Acosta, et al., 2018). In high-income countries, disease related to air pollution exposure results in increased health care costs that consume increasing portions of the annual health spending budget, with these health care costs likely to increase as further relationships between air pollution exposure and disease are identified (Landrigan, Fuller, Acosta, et al., 2018).

Further evidence is provided by recent studies demonstrating that lifelong exposure to pollution is accompanied by a drastic shortening of life. This varies on average between 3 – 6 months in modestly polluted countries such as the UK and the USA, to 1 – 2 years in highly polluted countries such as those in areas of Africa and Asia (Apte, Brauer, Cohen, Ezzati, & Pope, 2018; M. R. Miller & Newby, 2020).

There is however, cause for optimism as most pollution can be eradicated, and strategies to prevent or control pollution can be highly cost-effective. High-income and some middle-income countries have established legislation and issue regulations and advisory guidelines mandating clean air (Landrigan, Fuller, Acosta, et al., 2018) and substantial improvements and reductions in pollutant levels have already been observed (R. D. Brook et al., 2010). Pollution reduction and prevention has demonstrated sizeable net gains both for human health and the economy, and in locations where management approaches have been implemented to control air pollution, improvements have also been seen in population health (Institute for Health Metrics and Evaluation's Global Burden of Disease Project and the Health Effects Institute, 2017). This is evident in high-income countries where deaths related to pollution-mediated cardiovascular

(CV) and respiratory disease have been reduced, with the result of generating substantial economic gains (Landrigan, Fuller, Acosta, et al., 2018).

1.2 Statement of the problem

In recent years, exposure to environmental pollutants has been hypothesized as having an important role in the development and severity of cardiometabolic disease (CMD) (K. E. Cosselman, Navas-Acien, & Kaufman, 2015; Thomas Munzel, Schmidt, & Gori, 2015; T. Munzel et al., 2017a; T. Munzel et al., 2017b). Epidemiological and clinical studies indicate that air pollution can adversely affect sub-clinical cardiometabolic (CM) endpoints such as blood pressure (BP), blood lipid levels, glucose metabolism and vascular function (R. D. Brook et al., 2011; Dvonch et al., 2009; Lenters et al., 2010; Mehta et al., 2014; Shanley et al., 2016; B.-Y. Yang, Bloom, et al., 2018; B.-Y. Yang, Qian, et al., 2018). More recently it has been hypothesised that air pollution could constitute a novel and important CM risk factor in addition to established risk factors for CMD such as hypertension, dyslipidemia and diabetic related impaired glucose tolerance.

However, there are many issues that require clarification since many studies have used estimated stationary-site data or land use regression models as surrogates for ambient air quality, and in some cases, indoor air quality (IAQ) (Barnett et al., 2006; Bhatnagar, 2006; R. J. Delfino, Sioutas, & Malik, 2005; Lim & Thurston, 2019; J. Logue, Klepeis, Lobscheid, & Singer, 2014; Mudway, Kelly, & Holgate, 2020; Antonella Zanobetti & Schwartz, 2009).

Similar limitations exist when considering individual-level clinical cardiometabolic effects with outcomes such as ischemic heart disease, stroke, and type 2 diabetes mellitus (T2DM) commonly being derived through record linkage procedures, hospital admission/discharge registries, or by self-report (R. D. Brook, Cakmak, et al., 2013; R. J. Delfino et al., 2005; I. Eze et al., 2014; Milojevic et al., 2014; Mudway et al., 2020; C. A. Pope, 3rd et al., 2015; Stafoggia et al., 2013; Antonella Zanobetti & Schwartz, 2005). This data are then ordinarily linked to the ecologically derived exposure data to establish the directionality of a relationship leading to opportunities for the possibility of misclassification based on incorrect assumptions about individual-level pollutant characteristics (Wilson et al., 2005). Acknowledging these limitations, significant

associations have been described between ambient air quality and increased CM risk, at air pollution concentrations below recommended international standards (Bourdrel, Bind, Bejot, Morel, & Argacha, 2017; R. D. Brook et al., 2010; Pinault et al., 2016).

Whilst most published studies of human exposure relate to ambient air pollution, it is well recognised that exposure to air pollution occurs in both outdoor and indoor environments (Bourdrel et al., 2017; Karottki et al., 2013). Furthermore, adverse health effects including CM effects of indoor air, have been largely inferred from an exposure-response relationship generated from data on the CV impacts of outdoor air pollution (Brauner et al., 2008; Hadley, Baumgartner, & Vedanthan, 2018; Karottki et al., 2014).

Despite it being well reported of large portions of daily time being spent in the domestic environment in high-income countries, there are very few published studies that have been designed to objectively measure pre-clinical markers of CM risk with exposure to domestic air pollutants (Trenton Honda, Pun, Manjourides, & Suh, 2017; T. Honda, Pun, Manjourides, & Suh, 2018; Krassi Rumchev, Soares, Zhao, Reid, & Huxley, 2018). Rather, these relationships have been described by CV endpoint events such as heart failure, cardiac arrhythmias and arrest, stroke and mortality (Beelen et al., 2014; Bourdrel et al., 2017; Robert D. Brook, David E. Newby, & Sanjay Rajagopalan, 2017; Cohen et al., 2017; Collart, Dubourg, Leveque, Sierra, & Coppieters, 2018; R. J. Delfino et al., 2005; Fiordelisi et al., 2017; Hoek et al., 2013; Hoek. G., Brunekreef. B., Fischer. P., & J., 2001; Mudway et al., 2020), using methods described above.

1.3 Significance of the study

Cardiovascular disease (CVD) and T2DM are best regarded as chronic conditions with multiple factors influencing the pathophysiologic processes that are involved in the initiation and progression of these conditions.

However, the pathways by which CMD eventuates, and the role that air pollution exposure might play as a novel contributing risk factor in the development and augmentation of these conditions, is not well understood.

This current study is unique as it is believed to be the first study to examine the relationship between such an extensive selection of domestic indoor air pollutants (both particulate matter [PM] and gaseous) measured in real-time, with such a comprehensive

range of sub-clinical cardiometabolic biomarkers (both physical and blood/urine based).

The findings of this study will contribute to a better understanding of the relationship between residential IAQ, with selected functional intermediate outcomes related to CM risk, and in turn, may provide direction for future research.

Effective dissemination of the outcomes will raise awareness and potentially provide some insight regarding the relationship between exposure and CM response, particularly at low concentrations of air pollution. It is also hoped that this research will add to current understandings of whether thresholds exist for 'safe' exposure to indoor airborne pollutants. These findings may also contribute to the development of IAQ guidelines or advisory standards for indoor environments such as homes, schools, recreational buildings and even inside automobiles.

Additionally, understandings of potential effects of exposure to indoor air pollutants will be especially important to enable the prevention and possibly the treatment of CMD, and support the application of appropriate policies designed to protect public health (K. E. Cosselman et al., 2015).

1.4 Study aim and objectives

The primary aim of this study was to explore associations between exposure to selected residential indoor air pollutants with 24-hour, daytime and nighttime BP, nocturnal BP dip and a range of 24-hour, daytime and nighttime central hemodynamic measures in apparently healthy, middle-aged adults.

The secondary aim was to investigate associations between exposure to residential indoor air pollutants with selected blood and urine biomarkers related to CM risk, and carotid-femoral pulse wave velocity (PWV).

1.4.1 Project hypothesis

In this study, it is hypothesised that in middle-aged individuals, acute exposure to some selected indoor air pollutants will be independently and adversely associated with a range of sub-clinical CM risk factors.

Objectives of the study include:

1. To concurrently measure in one 24-hour period:
    i. Indoor residential concentrations of total particulate matter (TPM), PM_{10}, PM_4, $PM_{2.5}$, PM_1, ultrafine particles (UFP) and gaseous pollutants including formaldehyde (HCHO), total volatile organic compounds (TVOC), nitrogen dioxide (NO_2), carbon monoxide (CO) and carbon dioxide (CO_2);
    ii. Outdoor residential concentrations of airborne TPM, PM_{10}, PM_4, $PM_{2.5}$ and PM_1;
    iii. Ambulatory BP and central hemodynamic indices including augmentation index (AIx), normalized AIx (AIx_{75}) augmented pressure (AP), pulse pressure (PP), mean arterial pressure (MAP) and nocturnal systolic and diastolic dip.

2. To determine the impact selected household characteristics and occupant activities have on indoor air pollutant concentrations.

3. To carry out a clinical assessment to determine levels of serum cholesterol (total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides [TG], non-HDL and TC/HDL), measures of glucose homeostasis (fasting glucose, glycosated haemoglobin [HbA1c]) and renal function (albumin, creatinine, albumin/creatinine ratio [ACR]), and to conduct a pulse wave analysis (PWA) to determine carotid-femoral pulse wave velocity (PWV).

4. To explore the associations between measured indoor air pollutants and sub-clinical cardiometabolic risk factors.

1.5 Structure of the thesis

This thesis is comprised of six chapters.

Chapter one provides general background material related to the history of air pollution exposure and its genesis as a risk factor for adverse human health outcomes. It also provides a perspective on air pollution exposure and its impact on health systems in the

context of its effect on health care spending. Finally, this first chapter outlines the study aim and objectives, and identifies existing gaps in knowledge.

Chapter 2 reviews the literature linking a range of adverse or sub-optimal intermediate CM outcomes, with air pollution exposure. Where possible, examples are used from studies of indoor air pollution exposure in high-income countries however, and perhaps more importantly, the review addresses only sub-clinical cardiometabolic outcomes relevant to this study and does not consider air pollution related mortality or endpoint CM events.

The third chapter outlines the study methodology including participant recruitment, inclusion and exclusion criteria, data collection and instrumentation specifications. It also includes details of the sample size calculation, methods of statistical analysis and data management.

In Chapter 4, the findings of the study are presented. Descriptive statistics related to participant health and domestic environment are outlined followed by a comprehensive statistical analysis of association between individual indoor air pollutants, and each sub-clinical cardiometabolic risk factor.

Chapter 5 provides discussion of the results and considers findings in the context of other similar studies, and associated literature from both Australian and international authors. This chapter also summarises strengths and limitations of this current study in comparison to other similar research.

The sixth and final chapter provides conclusions and future research recommendations arising from this study.

CHAPTER TWO – LITERATURE REVIEW

This chapter highlights the importance and wide-ranging impacts of air pollution exposure on human health, focusing on a range of sub-clinical cardiometabolic risk markers. It also provides detail about indoor air pollution exposure and cardiometabolic outcome variables relevant to this current study, and outlines what is already known about these relationships.

2.1 Introduction

Air pollution is now acknowledged as a major environmental issue and significant public health problem responsible for a growing range of deleterious effects on human health (R. D. Brook, 2017; R. D. Brook et al., 2010; F. J. Kelly & Fussell, 2015). Whilst the ultimate effect of air pollution on public health is to facilitate premature death (F. J. Kelly & Fussell, 2015), epidemiologic studies are more consistently providing evidence of the impact of air pollution exposure on important clinical endpoints that adversely affect respiratory (J. Anderson, Thundiyil, & Stolbach, 2012; Cohen et al., 2017; Das & Horton, 2018; Jaganathan et al., 2019; Landrigan, Fuller, Acosta, et al., 2018), cardiovascular (Adar et al., 2018; J. A. Araujo & Rosenfeld, 2015; D. G. Bell et al., 2017; Bourdrel et al., 2017) and metabolic health (Z. Chen et al., 2016; Chuang, Yan, & Cheng, 2010; Cong Liu et al., 2016; S. Lucht et al., 2019; S. A. Lucht et al., 2018).

2.2 Ambient air pollution

In today's urban environment, 'modern' ambient or outdoor air pollution is a highly complex and dynamic mixture of PM, semi-volatile liquids and gaseous pollutants including nitrogen oxides (NO_x), sulphur dioxide (SO_2), ozone, volatile organic compounds (VOC), carbon dioxide (CO_2) and carbon monoxide (CO) (Figure 2.1) (Bourdrel et al., 2017; R. D. Brook et al., 2004; Robert D. Brook et al., 2017; Hadley

et al., 2018; F. J. Kelly & Fussell, 2015; M. R. Miller & Newby, 2020; Mudway et al., 2020).

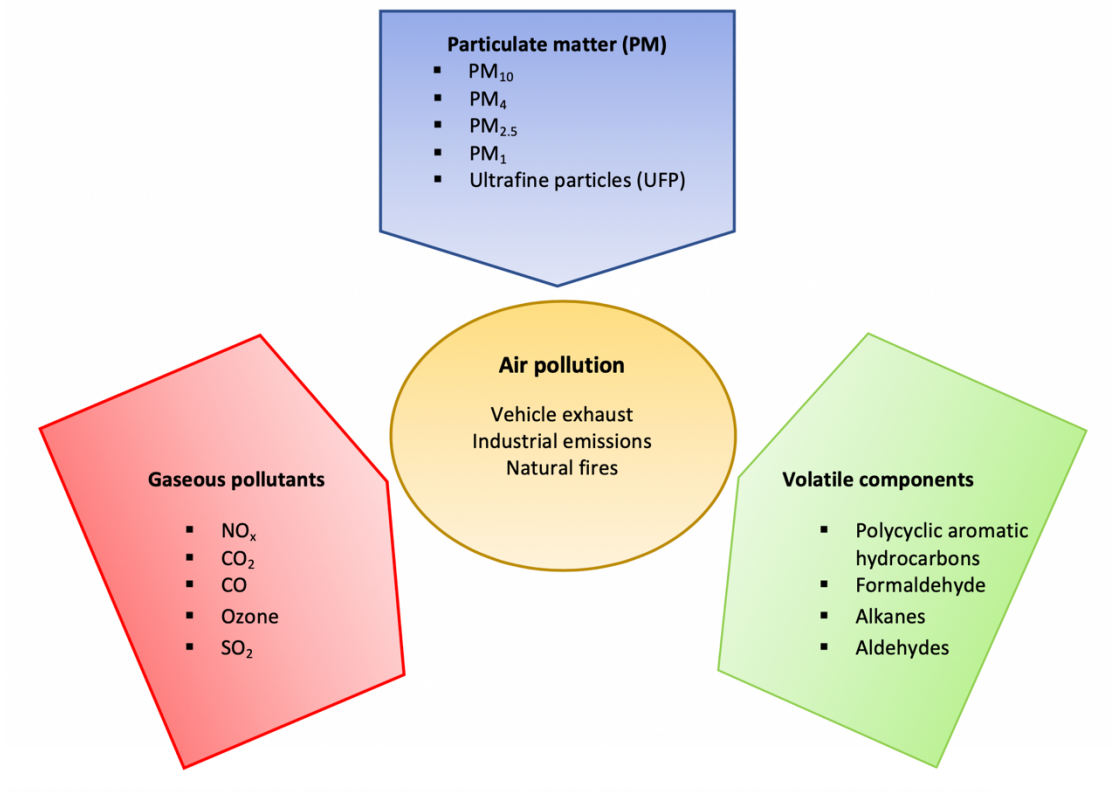

Figure 2. 1 *A simple schematic diagram demonstrating a complex mix of components that air pollution can comprise.*

Included in the mix are organic and inorganic components from biogenic (i.e., natural and living), anthropogenic (i.e., human-made) and geogenic (i.e., natural and non-living) sources (Environment Australia, 2017a; Schulz et al., 2019) that are generated from regulated and non-regulated human activities. This leads to very different exposure mixtures (International Agency for Research on Cancer, 2016) that vary spatially and temporally (Cohen et al., 2017). Atmospheric transformations along with geographical meteorology associated with a region, mean that in any location, air pollution will have origins from local sources, and also from sources that affect air quality regionally and even globally (International Agency for Research on Cancer, 2016). The characterisation of chemical components in the mix however, can be useful in determining the origins of the air pollution (Abdullahi, Delgado-Saborit, & Harrison, 2013).

2.2.1 Components of ambient air pollution

PM is the component of air pollution that includes solid particles, liquid droplets or combinations of both that vary in size, shape, number, surface area, solubility, origin and chemical composition (Capon & Wright, 2019; Nasir & Colbeck, 2013; C. A. Pope & Dockery, 2006).

PM is commonly classified by its chemical composition (R. D. Brook et al., 2010; International Agency for Research on Cancer, 2016) which may comprise acids, organic chemicals, metals, soil and dust particles (Nasir & Colbeck, 2013). However, more commonly it is classified according to size (Hadley et al., 2018). PM_{10} or "thoracic particles" are defined as particles having an aerodynamic diameter (d_a) ≤ 10 µm, $PM_{10\text{-}2.5}$ or "coarse particles" have an d_a of between 10 µm and 2.5 µm, $PM_{2.5}$ or "fine particles" with an d_a < 2.5 µm, PM_1 are particles with a d_a < 1 µm, and ultrafine particles (UFP) have an d_a < 0.1 µm (Figure 2.2) (R. D. Brook et al., 2010; Hadley et al., 2018; M. R. Miller & Newby, 2020; Mudway et al., 2020).

Total particulate matter (TPM) or total suspended particles generally describes the aggregated combination of all PM sizes and represents d_a < 100 µm (C. A. Pope & Dockery, 2006; Wilson et al., 2005).

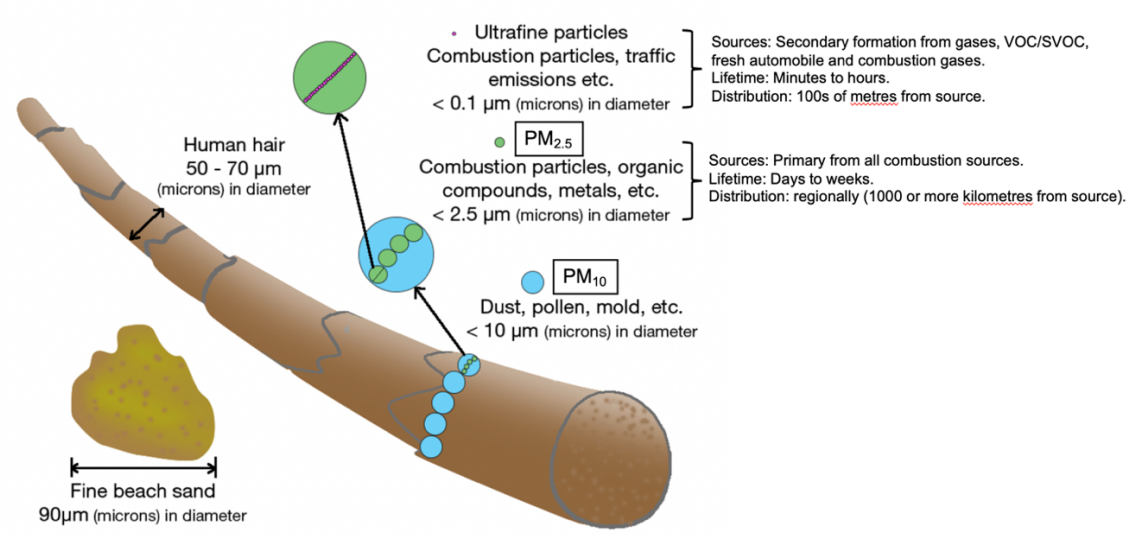

Figure 2. 2 *Particulate matter size fractions.*

[Image adapted from: VFA Solutions (2017)]

Further complicating the classification of air pollution is that some pollutants move between condensed (particle) solid phases and gaseous phases (e.g., VOC) and can be classified as primary or secondary particles (Abdullahi et al., 2013; P. M. Mannucci, Harari, & Franchini, 2019; Millar et al., 2010). Primary particles are emitted directly from a source (primary PM) into the atmosphere in a solid, liquid, or vapour that can quickly condense into fine particles.

Secondary particles are formed in the atmosphere from chemical reactions involving primary particles, gaseous emissions and other secondary particles (e.g., ozone) (Abdullahi et al., 2013; International Agency for Research on Cancer, 2016; P. M. Mannucci et al., 2019; Millar et al., 2010). Secondary particle formation is dynamic and can occur over minutes to days making identification of their original emission source difficult (Millar et al., 2010). Additionally, some pollutants can be both primary and secondary (e.g., formaldehyde) (International Agency for Research on Cancer, 2016).

2.2.2 Sources of particulates

Major sources of ambient PM in urban areas are associated with fossil fuel combustion primarily from traffic emissions or residential heating, industry emissions and mineral dusts from agriculture (Bourdrel et al., 2017; F. J. Kelly & Fussell, 2015; P. M. Mannucci et al., 2019; Wilson et al., 2005).

Larger particles such as $PM_{10,}$ predominantly originate from suspension or re-suspension of dust, soil, or other crustal materials and can also include sea salts, pollen, mould and spores (C. A. Pope & Dockery, 2006).

Fine particles < 2.5 μm in diameter ($PM_{2.5}$), largely originate as direct emissions from combustion sources (metals, carbon species), non-combustion sources or secondarily, involving atmospheric reactions (nitrates, sulphates) (R. D. Brook, D. E. Newby, & S. Rajagopalan, 2017). These sources include vehicle exhaust, wood and coal burning used in domestic heating, wildfires and prescribed burns, and industrial sources (Hadley et al., 2018). $PM_{2.5}$ persist longer (airborne days) and can be transported hundreds of kilometres impacting large areas, all of which is influenced by geography and meteorological conditions (R. D. Brook et al., 2017).

UFP directly derive from and are at highest concentrations nearby (100m – 400m) to combustion processes in urban settings and motor vehicles. They also arise through secondary photochemical formations (Bhangar, Mullen, Hering, Kreisberg, & Nazaroff, 2011; R. D. Brook et al., 2017; Brunekreef & Holgate, 2002). Primary UFP are generally a short-lived species (airborne minutes to hours) (R. D. Brook et al., 2017), however they can rapidly grow into larger complex aggregates through coagulation and/or condensation (C. A. Pope & Dockery, 2006).

2.2.3 Metrics of PM

Concentrations of PM are typically measured by mass per volume of air ($\mu g/m^3$), with PM_{10} and $PM_{2.5}$ being the two most commonly used mass-based metrics (Millar et al., 2010). UFP are included in concentrations of PM_{10} and $PM_{2.5}$ but typically contribute an insignificant fraction to the mass whereas they dominate particle numbers (Figure 2.3) (Newby et al., 2015). Counting particle numbers per cubic centimetre ($particles/cm^3$) is more routine for UFP than measures of mass per volume of air (R. D. Brook et al., 2010; Millar et al., 2010).

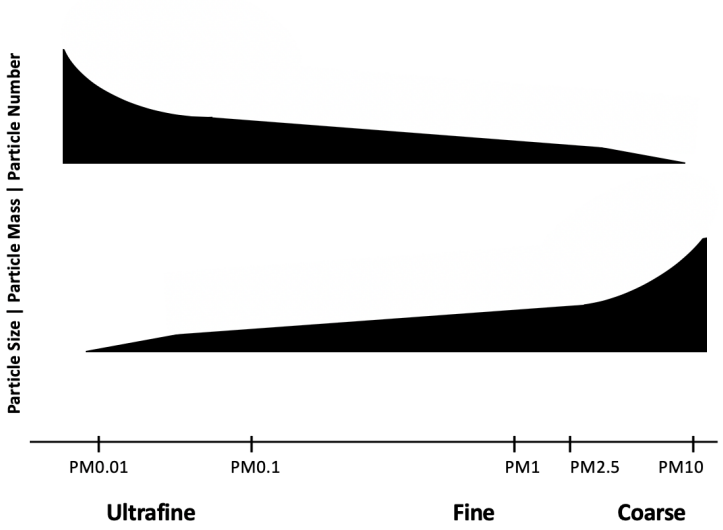

Figure 2. 3 *A hypothetical mixed particle distribution.*
[Image adapted from Anderson et al,. (2012)]

2.3 Indoor air pollution

Whilst most published studies of human exposure relate to ambient air pollution (Afsar et al., 2019; R. D. Brook, Bard, et al., 2008; R. D. Brook et al., 2011; Robert D. Brook et al., 2017; Yuanyuan Cai et al., 2016; S.-Y. Chen, Chu, Lee, Yang, & Chan, 2018; Cicoira, 2018; Jaganathan et al., 2019; Kephart et al., 2020; Riant et al., 2018) or occupational settings (Bortkiewicz et al., 2014), it is well recognized that exposure to air pollution occurs in both outdoor and indoor environments (Bourdrel et al., 2017). Although we accept that inhalation exposure to airborne contaminants can occur in both environments, it is not known whether indoor air pollution has an equal or greater impact on health when compared with that of outdoor air pollution (Lin, Chuang, Liu, Chen, & Chuang, 2013). It is considered however, that indoor exposures are a major contributor to total personal exposure (Janssen et al., 1998) with Morawska et al. (2013) concluding in a review of the literature that up to 30% of the burden of disease from air pollution exposure can be attributed to particles that are generated indoors.

Importantly, indoor air quality issues are increasingly acknowledged as a significant risk factor for human health in low-, middle- and high-income countries alike (World Health Organisation, 2010). It is also critical to recognise the importance of domestic settings in human exposure as studies on time-activity patterns conducted in high-income countries such as the USA, Canada, Germany and United Kingdom has found that almost 90% of time is spent indoors, and of this indoor time, approximately two-thirds is spent in the home (Brasche & Bischof, 2005; Lai et al., 2004; Leech, Nelson, Burnett, Aaron, & Raizenne, 2002; Newby et al., 2015; Schweizer et al., 2007).

2.3.1 Sources of indoor air pollution

Indoor air pollution is a heterogenous mixture of particles and gases with concentrations affected by infiltrating outdoor particles (Bennett & Koutrakis, 2006; Bhangar et al., 2011; F. J. Kelly & Fussell, 2019), emissions from indoor generating sources (World Health Organisation, 2010), air exchange rates and particles formed indoors through reactions and secondary processes of particles originating from both indoor and outdoor sources (F. J. Kelly & Fussell, 2019; Morawska et al., 2017; Morawska, He, Hitchins, Gilbert, & Parappukkaran, 2001).

In high-income countries such as Australia, the use of gas and electric cooking appliances and heating and cooling appliances, furniture, dust re-suspension and indoor combustion of solid fuels (e.g., wood, coal) significantly contribute to both gaseous and particulate indoor air pollution (Morawska et al., 2013; Morawska et al., 2017; L. Wallace, 2006, 2012). In contrast, main sources of indoor air pollution in low- and middle-income countries typically involves cooking and heating using solid fuels such as dung, crop residues or wood in homes with poor ventilation (Balmes, 2019; J. Baumgartner et al., 2018; J. Baumgartner & Clark, 2016; Clark et al., 2019; Peter Franklin, Tan, Hemy, & Hall, 2019; Kephart et al., 2020; S. Rajkumar et al., 2018; Sarah Rajkumar et al., 2019; Young et al., 2019).

2.3.2 Components of indoor pollution

2.3.2.1 Particulate matter

Similar to outdoor PM, the size and characteristics of indoor PM are dependent on their originating sources and post emission processes. This makes the composition and toxicity of indoor pollution very complex, with particles originating from indoors and outdoors representing different sources and size distributions and also different chemical compositions and biological effects (Diapouli, Chaloulakou, & Koutrakis, 2013; F. J. Kelly & Fussell, 2019; Morawska et al., 2017). Whilst the evidence is unconvincing of a difference in the hazardous nature of indoor-originating PM as compared with those from outdoors, it has been described in IAQ studies that concentrations reported in typical indoor microenvironments such as homes are significant, and may often exceed the equivalent outdoor concentrations (Diapouli et al., 2013; Rojas-Bracho, Suh, Catalano, & Koutrakis, 2004; World Health Organisation, 2010).

2.3.2.2 Volatile organic compounds

Volatile organic compounds (VOC) are a large, diverse and common group of chemical pollutants that are reasonably abundant in domestic indoor air. Key examples of VOC include formaldehyde, benzene, toluene, xylene, polycyclic aromatic hydrocarbons (PAHs) and other classes of which many have known health effects (R. D. Brook et al., 2010; International Agency for Research on Cancer, 2016; J. M. Logue, McKone,

Sherman, & Singer, 2011; W.-T. Tsai, 2019; US EPA, 2017). Major indoor sources of VOC include building materials and finishes (primarily flame retardants) including paints and floor coverings (made of or containing flexible plastics such as vinyl), engineered wood products, cleaning products and fragranced consumer products (Goodman et al., 2017; W.-T. Tsai, 2019; US EPA, 2017), however ventilation rates along with the humidity and temperature of a home, can also affect the levels of VOC indoors (Cakmak et al., 2014; Langer et al., 2016).

Many VOC detected in indoor environments are at low concentrations, however concentrations due to indoor sources vary widely and are dependent on occupant behaviours (Hoskins, 2011; Wolkoff, 1999). Although some guidelines are provided internationally for individual VOC (Settimo, Manigrasso, & Avino, 2020), in Australia, regulatory guidelines for acceptable indoor VOC concentrations do not currently exist. However published studies indicate levels of VOC are often higher indoors than outdoors (Cheng et al., 2016; Goodman et al., 2017; Molloy et al., 2012; K. Rumchev, Spickett, Bulsara, Phillips, & Stick, 2004; US EPA, 2017).

Exposures to some species of VOC have been associated with acute and chronic adverse health effects including sensory irritation, skin irritation upon dermal contact, headaches, nausea, breathing difficulties, decreased lung function, asthma risk, cancer (Cakmak et al., 2014; R. J. Delfino et al., 2005; Mendell, 2007; K. Rumchev et al., 2004; W.-T. Tsai, 2019; US EPA, 2017) and more recently with several markers of cardiovascular risk (Everson et al., 2019).

2.3.2.3 Formaldehyde

Formaldehyde (HCHO) is one of the best known and common VOC and is one of the few indoor gaseous air pollutants that can be readily measured (US EPA, 2017). It is a colourless, flammable compound found in the environment that is formed primarily from both natural and anthropogenic activities. Indoor sources are vast and include pressed wood products (particleboard, plywood and medium density fibreboard), furnishings, paints, wallpaper glues and adhesives, varnishes and lacquers, household cleaning products, cosmetic and consumer products such as liquid soaps, shampoos and nail varnishes, electronic equipment and combustion processes (Mendell, 2007;

Nielsen, Larsen, & Wolkoff, 2013; Salthammer, Mentese, & Marutzky, 2010; W.-T. Tsai, 2019; US EPA, 2017; Wolkoff, 2008; World Health Organisation, 2010).

The International Agency for Research on Cancer (IARC) has classified HCHO as a Group 1 carcinogen (known human carcinogen) (IARC, 2012) and the World Health Organisation (WHO) has indicated that indoor concentrations may be high enough to cause adverse health outcomes (World Health Organisation, 2010).

Higher indoor concentrations of HCHO have been associated with a range of acute and chronic adverse health effects including sensory irritation of the eyes and upper airways, asthma, airway inflammation, chronic bronchitis, increased wheeze and adverse effects on lung function and reduced birth weights with maternal exposure (P. Franklin, Dingle, & Stick, 2000; Peter Franklin et al., 2019; Golden, 2011; IARC, 2012; Mendell, 2007; Nielsen et al., 2013; Nielsen, Larsen, & Wolkoff, 2017; K. B. Rumchev, Spickett, Bulsara, Phillips, & Stick, 2002; W.-T. Tsai, 2019; Wolkoff & Nielsen, 2010; World Health Organisation, 2010).

2.3.2.4 Nitrogen Dioxide

Nitrogen dioxide (NO_2) is a volatile, reddish-brown gas with a pungent odour perceptible from a concentration of 0.1 ppm. Indoor levels can vary widely dependent on the presence of indoor sources combined with the characteristics and furnishings of the residence. Indoor sources of NO_2 include cigarette smoke and gas-, wood-, kerosene- and coal-burning appliances such as stoves, ovens, space and water heaters and fireplaces, particularly unflued or poorly maintained appliances. It can be introduced indoors by the infiltration of outdoor air and it has also been shown that vehicle exhaust containing NO_2 may infiltrate a home from an attached garage (World Health Organisation, 2010). In homes where there are no indoor NO_2 sources, indoor levels will be lower than outdoor levels. Furthermore, indoor levels are typically higher in winter than in summer which is probably due to the increased use of heating appliances and reduced ventilation rates (García Algar et al., 2004).

NO_2 does not appear to have a direct effect on cardiovascular pathologies (Hesterberg et al., 2009) although with hospital admissions, NO_2 has been associated with a range of cardiovascular events including raised risk for arrhythmias, atrial fibrillation, myocardial infarction (MI) and heart failure (Collart et al., 2018; Milojevic et al., 2014).

2.3.2.5 Carbon Monoxide

Carbon monoxide (CO) is a colourless, odourless and tasteless gas that is produced indoors by combustion sources such as cooking and heating. It is also introduced indoors through the infiltration of outdoor air although in high-income countries, the most common source is from faulty, incorrectly installed, poorly maintained or poorly ventilated cooking and heating appliances that burn fossil fuels. This includes wood-burning fireplaces and gas burners, although cigarette smoke, incense burning and infiltrating exhaust fumes from garages attached directly to residences are also major indoor sources (World Health Organisation, 2010).

Headaches, dizziness, vomiting and loss of consciousness have been reported with acute exposure to high levels of CO (> 100 ppm) (Northcross, Hwang, Balakrishnan, & Mehta, 2015). However, the effects of chronic exposure to low dose CO such as might be seen in indoor environments is unclear (Northcross et al., 2015), although epidemiological studies have reported that maternal exposure increases the incidence of low birth weight and perinatal deaths (Salam et al., 2005) and contributes to hospital admissions for cardiovascular events including congestive heart failure and stroke (H. Liu et al., 2018; World Health Organisation, 2010).

2.4 Air quality guidelines and standards

2.4.1 Ambient air

Modern-day air quality standards are designed for the protection of human health for all people and in particular for those considered susceptible. However, international air quality guidelines and standards exist for only a selected number of ambient air pollutants (Hooper & Kaufman, 2018).

In Australia, air quality in metropolitan centres is classified as ‘good’ or ‘very good’. The National Environment Protection Measure for ambient air quality (NEPM - AAQ) sets legally binding national standards for ambient air that are designed for the protection of human health (Capon & Wright, 2019; Keywood, Emmerson, & Hibberd, 2016). Several ambient air ‘toxics’ including CO, NO_2, photochemical oxidants (including ozone), SO_2, lead, PM_{10} and $PM_{2.5}$ have been provided national ambient

standards by the NEPM - AAQ (National Environment Protection Council, 2016a) (Table 2.1).

Nationally, the standard for PM_{10} is rarely exceeded however the standard for $PM_{2.5,}$ which until 2016 was an advisory limit only, is frequently exceeded because of extreme events such as bushfires, prescribed burns, smog, dust storms and the use of residential wood heaters (Environment Australia, 2017a; Keywood et al., 2016).

2.4.1.1 Limitations of the standards-based approach

The application of a standards-based approach however has limitations as there is no evidence to indicate that there is a concentration threshold below which exposures can be considered safe at the population level (Barnett, 2014; R. D. Brook et al., 2017; Capon & Wright, 2019; Environment Australia, 2017a; Keywood et al., 2016; M. R. Miller & Newby, 2020; World Health Organisation, 2013). In fact, data strongly indicates that effects have no threshold within the studied range of ambient concentrations, human health effects can occur at levels close to background concentrations, and that they follow a mostly linear concentration-response function (World Health Organisation, 2013). It is also critical to note that while high and extreme pollution concentrations are well-established as a catalyst for adverse human health events (R. D. Brook et al., 2016; Xie et al., 2018; Y.-R. Yang, Chen, Chen, & Chan, 2017; P. Zhang et al., 2011; Zhao et al., 2014), the relationship between exposure and adverse health effects is now being established at low levels of exposure (Bourdrel et al., 2017). This has been seen more recently where a notable increase in studies evaluating health effects at low concentrations, such as those which might be experienced in higher income/cleaner countries, have found that air pollution exposure remains capable of promoting CV events and adversely influencing BP, even at exposure levels that are below current environmental and ambient air quality guidelines (R. D. Brook, 2017; R. D. Brook et al., 2017; Robert D. Brook et al., 2017; R. D. Brook et al., 2010; R. D. Brook, Weder, & Rajagopalan, 2011; Everson et al., 2019).

As a result, concerns have been raised about the use of air quality standards, including the Australian NEPM - AAQ, which are frequently misinterpreted to infer levels above an advocated standard are potentially unsafe and those below the standard are ‘safe’ (Barnett, 2014).

2.4.2 Indoor air

Legislation relating to air quality in high-income countries is traditionally based upon ambient outdoor concentrations which potentially leads to insufficient protection for individuals who spend most of their time indoors where concentrations of some pollutants can be much higher than outdoor levels (Abdullahi et al., 2013).

No specific standards are available for IAQ in Australia, although Canada, Japan, and several European countries have introduced guidelines for selected pollutants and a number of individual VOCs in indoor environments (Settimo et al., 2020). Importantly however, the WHO has acknowledged the unique role IAQ plays as a health determinant and important risk factor for human health. In 2010, it was noted that the impact of indoor air pollutants to human health could far exceed that imposed by exposure to outdoor air pollutants and as such the WHO produced a set of recommended limits for health-harmful concentrations of key air pollutants that are known to have indoor sources (World Health Organisation, 2010). Some of these indoor chemical substances for which guidelines have been set include benzene, carbon monoxide, formaldehyde, naphthalene, polycyclic aromatic hydrocarbons, nitrogen dioxide, radon, trichloroethylene and tetrachloroethylene.

Regulatory guidelines for acceptable pollutant concentrations within domestic indoor environments still do not currently exist in Australia (Environment Australia, 2017b). Whilst there are regulations and codes that address IAQ, these apply to workplace situations, commercial premises and public buildings, rather than to residential dwellings (Environment Australia, 2017b).

In 1992, national IAQ guidelines were recommended by the Australian National Health and Medical Research Council (NHMRC), however they were rescinded in 2002 (NHMRC, 2016) and continue to be used discretionarily by researchers, along with international guidelines (Table 2.1).

Table 2. 1 Australian and international standards and guidelines for ambient and indoor air quality.

	Pollutant guidelines					
	NEPM 2004/2016[a]	**WHO 2005[b]**	**EU 2008/50[c]**	**NHMRC 1992[d]**	**WHO 2010[e]**	**Health Canada[f]**
TPM		dose-response		90 µg/m^3		

exposure period				annual mean		
PM_{10}	50 µg/m^3	50 µg/m^3	50 µg/m^3			
exposure period	1 day	1 day	1 day			
$PM_{2.5}$	25 µg/m^3	25 µg/m^3				'as low as possible'
exposure period	1 day	1 day				
HCHO	50 µg/m^3 (0.04 ppm)	100 µg/m^3		120 µg/m^3 (0.1 ppm)	100 µg/m^3 (0.081 ppm)	123 µg/m^3 (0.1 ppm)
exposure period	1 day	0.5 h		ceiling	0.5 h	1 h
TVOC		n/a		500 µg/m^3		
exposure period				1 h		
CO	10 000 µg/m^3 (9 ppm)	10 000 µg/m^3 (9 ppm)		10 000 µg/m^3 (9 ppm)	7000 µg/m^3	11 500 µg/m^3 (10 ppm)
exposure period	8 h	8 h		8 h average	24 h	24 h
NO^2	0.12 ppm	200 µg/m^3 (0.1 ppm)	200 µg/m^3 (0.1 ppm)	320 µg/m^3 (0.16 ppm)	200 µg/m^3 (0.1 ppm)	170 µg/m^3 (0.09 ppm)/20 µg/m^3 (0.011 ppm)
exposure period	1 h	1 h	1 h	1 h	1 h	1 h/24 h

[a] - National Environment Protection Council (2004, 2016a, 2016b); [b] - World Health Organisation (2005); [c] European Union air quality directives (2008/50/EC Directive on Ambient Air Quality and Cleaner Air for Europe (European Environment Agency, 2016); [d] - NHMRC (2016) rescinded IAQ guidelines; [e] - World Health Organisation (2010) guidelines for indoor air pollutants; [f] - Health Canada residential indoor air quality guidelines (Health Canada, 2020); TPM – total particulate matter; µg/m^3 – micrograms per cubic metre; PM_{10} – particulate matter with an aerodynamic diameter < 10 µg/m^3; $PM_{2.5}$ – particulate matter with an aerodynamic diameter < 2.5 µg/m^3; HCHO – formaldehyde; µg/m^3 - micrograms per cubic metre; ppm – parts per million; TVOC – total volatile organic compounds; CO – carbon monoxide; NO_2 – nitrogen dioxide; * these guidelines are currently under revision with an expected publication date in 2020.

2.5 Air pollution as a health hazard

The impact of air pollution exposure on human health has been the subject of considerable scientific effort in recent years with large volumes of recent work supporting that ambient air pollution exposure may adversely affect a range of clinical health endpoints. Examples of these endpoints include blood pressure (BP), vascular function, glucose and lipid metabolism, endothelial function and the progression of atherosclerotic lesions (D. G. Bell et al., 2017; Bourdrel et al., 2017; Brauner et al., 2008; R. D. Brook et al., 2011; R. J. Delfino et al., 2005; R.J. Delfino, Staimer, & Vaziri, 2011; Dvonch et al., 2009; Karottki et al., 2014; Lenters et al., 2010; Mehta et al., 2014; Rajagopalan, Al-Kindi, & Brook, 2018; Schulz et al., 2019; Shanley et al., 2016; X. M. Wu et al., 2019; B.-Y. Yang, Bloom, et al., 2018; B.-Y. Yang, Qian, et al., 2018).

Various gaseous pollutants and PM have both been implicated as potentially harmful for health (R. D. Brook et al., 2010; F. J. Kelly, 2003; F. J. Kelly & Fussell, 2012, 2015;

Sanidas et al., 2017; Weichenthal, 2012). However, the most severe effects have been attributed to ambient PM, with their size and ability to carry a broad range of toxic substances reported to be directly linked to their potential for causing health-related problems (Brauner et al., 2008; R. J. Delfino et al., 2005; R.J. Delfino et al., 2011; Karottki et al., 2014; F. J. Kelly & Fussell, 2012, 2015; F. J. Kelly & Fussell, 2019; P. Mannucci, Harari, Martinelli, & Franchini, 2015; Rohr & Wyzga, 2012; Sanidas et al., 2017; Uzoigwe, Prum, Bresnahan, & Garelnabi, 2013; Weichenthal, 2012). Data demonstrates the existence of a mostly linear concentration-response function between PM and human disease, and that the prevalence of these diseases can be decreased or eliminated by removal from a PM-rich environment (J. Anderson et al., 2012; F. J. Kelly & Fussell, 2015; F. J. Kelly & Fussell, 2019).

Both short- and long-term air pollution exposures have been implicated as having roles in adverse outcomes for human health, with a rapidly expanding body of evidence linking air pollution with an increased risk of respiratory conditions (e.g., reduced lung function, asthma, chronic obstructive pulmonary disease, lung cancer), cardiovascular disease (e.g., myocardial infarction, heart failure, atherosclerosis, hypertension) and more recently, metabolic dysfunction (e.g., insulin resistance, diabetes) (J. Anderson et al., 2012; Haberzettl, O'Toole, Bhatnagar, & Conklin, 2016; F. J. Kelly, 2003; F. J. Kelly & Fussell, 2012; F. J. Kelly & Fussell, 2019; Li et al., 2018; S. Lucht et al., 2019; P. Mannucci et al., 2015; Rohr & Wyzga, 2012).

Furthermore, harmful health effects have been observed to occur not only after acute exposure to elevated concentrations of particulate and gaseous air pollutants, but also after low concentration short-term and long-term exposure (R. D. Brook, Xu, et al., 2013; Franchini & Mannucci, 2012; Song et al., 2016; Stafoggia et al., 2013; Thiering et al., 2013).

2.5.1 Health effects at low concentration exposures

Crouse and colleagues (2012), investigated the risk of adverse CV outcomes from long-term exposure to low concentrations of $PM_{2.5}$. In this cohort study of 2.1 million non-immigrant Canadians, it was reported that ischemic heart disease deaths significantly increased by 30% (per 10 $\mu g/m^3$) despite average concentrations of $PM_{2.5}$ (mean 8.7 $\mu g/m^3$; IQR: 6.2 $\mu g/m^3$) being well below current relevant standard levels.

In other studies, long- and short-term exposures to ambient gaseous pollutants have been associated with hemodynamic changes including BP, even at low exposure concentrations (Bolden, Kwiatkowski, & Colborn, 2015; Franchini & Mannucci, 2012; Weichenthal, Hatzopoulou, & Goldberg, 2014; B.-Y. Yang, Qian, et al., 2018).

In a recent South African (Cape Town) longitudinal study of 61 healthy females, Everson and colleagues (2019), found BP (both systolic BP and diastolic BP) was positively associated with NO_2 at relatively low levels of personal air pollution exposure when compared to international standards (Everson et al., 2019).

R. D. Brook, Xu, et al. (2013) provides further support on the importance of relatively low levels of air pollution exposure. In this prospective cohort study, ambient level $PM_{2.5}$ exposure (daily 4 - 5 hours over 5 consecutive days) was measured in 25 apparently healthy adults with impaired glucose tolerance from rural areas of Michigan, USA. The study findings showed that small elevations in ambient $PM_{2.5}$ concentrations may reduce metabolic insulin sensitivity after short periods even at low exposure levels (mean level ≅ 11.5 $\mu g/m^3$), and thus potentially contribute to the development of T2DM (R. D. Brook, Xu, et al., 2013).

Additional evidence comes from a Swedish cohort which demonstrated that exposure to NO_2 at levels below current WHO air quality guidelines during pregnancy was associated with gestational diabetes and pre-eclampsia (Malmqvist, Jakobsson, Tinnerberg, Rignell-Hydbom, & Rylander, 2013).

It is however important to note that at lower levels of pollution, these associations are not consistently observed. A nationwide study in the USA found a significant association between air pollution and HbA1c (Trenton Honda et al., 2017) where, in contrast, a study of a city and two rural areas in Southern Germany did not (Wolf et al., 2016).

2.5.2 Particle size and penetration levels

Particle size is critical when considering potential health impacts of PM (Capon & Wright, 2019), as the deposition of inhaled particles in the respiratory tract depends mainly on breathing pattern and their size. Particles greater than 10 μm are filtered through the nose but are too large to reach the deeper respiratory tract (Capon & Wright,

2019). These particles are caught in the mucous lining of the nose and throat and are removed through normal breathing activities. Particles with a diameter of 10 µm or less are small enough to penetrate deep into the lower respiratory tract to be deposited in the lungs during normal nasal breathing (Capon & Wright, 2019; Fiordelisi et al., 2017).

Smaller diameter particles with a $d_a < 2.5$ µm, and UFP with a $d_a < 0.1$ µm, are generally considered more hazardous to human health due to their capacity to penetrate deep into the small airways of the respiratory system, bypassing alveolar clearing mechanisms to deposit on the alveoli – the tiny sacs in the lungs where gas exchange occurs (Figure 2.4) (Brunekreef & Holgate, 2002; Fiordelisi et al., 2017; P. M. Mannucci et al., 2019; Morman & Plumlee, 2013). These smaller diameter particles can also be absorbed into the circulatory system through alveolar capillaries and may reach the blood stream and organs (including the placenta and brain) through translocation across biological membranes, posing an even greater risk due to systemic health impacts (Fiordelisi et al., 2017; P. M. Mannucci et al., 2019; M. R. Miller & Newby, 2020; World Health Organisation, 2018).

Particle size and estimated penetration levels are shown at Figure 2.4.

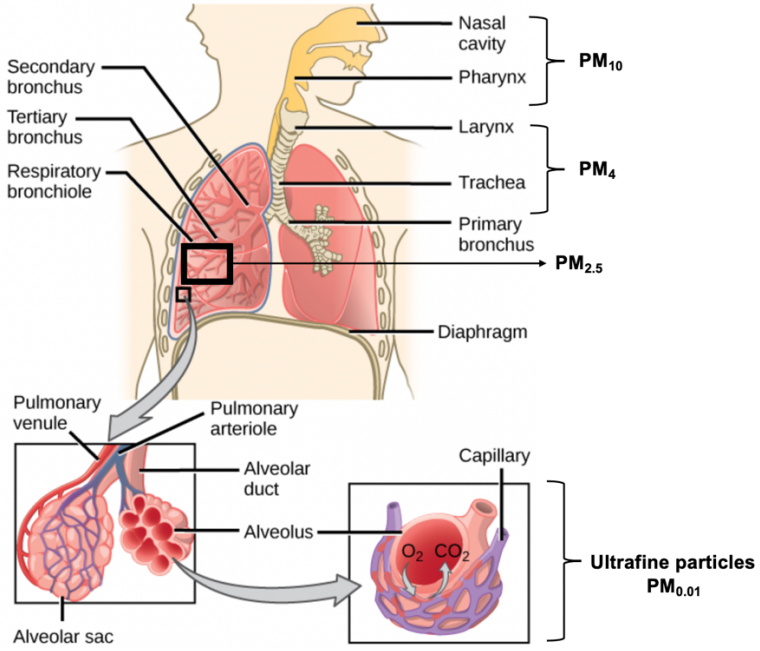

Figure 2. 4 *Particle size and estimated penetration level in the respiratory tract.*

Further contributing to the risk is that relative to larger particles, those with a $d_a < 2.5$ μm can remain suspended for longer periods of time, are continuously formed in the atmosphere, can penetrate more readily into indoor environments and are transported over much longer distances (Capon & Wright, 2019; C. A. Pope & Dockery, 2006). Whilst most current studies have focused on the human health effects of PM_{10} and $PM_{2.5}$, it has been hypothesized that the smaller particle sizes, which result in increased degrees of lung penetration and a larger reactive surface area, might lead to greater toxicity per unit mass than the larger diameter particle fractions (Figure 2.5) (Brunekreef & Holgate, 2002; Capon & Wright, 2019; R. J. Delfino et al., 2005; P. M. Mannucci et al., 2019; M. R. Miller & Newby, 2020).

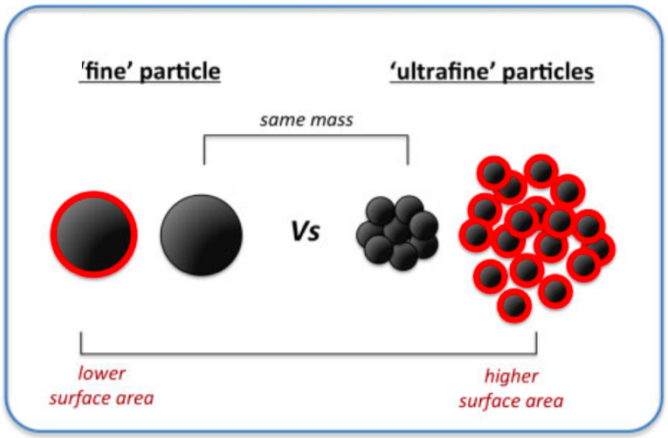

Figure 2. 5 *Comparison of surface area between $PM_{2.5}$ and UFP.*
[Image adapted from: M. R. Miller and Newby (2020)]

2.6 Air pollution-mediated cardiometabolic health effects

A growing body of epidemiological and clinical evidence has implicated ambient air pollution as an emerging risk factor for adverse outcomes related to cardiovascular (R. D. Brook et al., 2011; R. D. Brook et al., 2010; Rabito et al., 2020) and metabolic (L. Chen et al., 2016; Trenton Honda et al., 2017; Kramer et al., 2010; Renzi et al., 2018; Shamy et al., 2018) health. This evidence has put ambient air pollution among the modifiable risk factors for cardiovascular and metabolic diseases, as already recognized

by the American Heart Association (R. D. Brook et al., 2010) and subsequently by the European Society of Cardiology (Newby et al., 2015).

Although specific pathophysiological mechanisms that might contribute to associations between air pollution exposure and adverse cardiometabolic outcomes remain unclear, evidence from animal (Q. Sun et al., 2009; Ying et al., 2014) and epidemiologic studies (Cicoira, 2018; B. A. Franklin, Brook, & Arden Pope, 2015; Rajagopalan et al., 2018; Rajagopalan & Brook, 2012; Qinghua Sun, Hong, & Wold, 2010) contribute to confirming a role in the development and augmentation of CMD.

However, most of these investigations have relied upon outdoor pollutant concentrations as surrogates of human exposures (Bennett & Koutrakis, 2006) and considering that individuals spend the majority of their time indoors, human exposures to pollutants of outdoor origin may not be equal to indoor particle concentration levels (Abt, Suh, Catalano, & Koutrakis, 2000).

It is also important to note that our current understandings of air pollution mediated cardiometabolic outcomes and disease is mostly derived from ambient air pollution studies due to the paucity of data from indoor air pollution studies (Rajagopalan & Brook, 2012).

Furthermore, it is likely that many sub-clinical physiological changes occur in individuals in response to air pollution exposures that do not become overtly discernible as a CM condition or event (R. D. Brook et al., 2010). Therefore the illustration of some of the more subtle responses (i.e., intermediate or sub-clinical outcomes) supports the likelihood of the observable outcome associations and provides understanding into potential mechanisms whereby exposure to air pollution might precede and mediate CMD's (R. D. Brook et al., 2010).

Several potential biological pathways have been hypothesized that can be triggered by direct effects of pollutants on the cardiometabolic system (Fiordelisi et al., 2017). However, in terms of cardiometabolic risk, it is unlikely that a single biomarker or measure relates to a health outcome with a specific exposure because a group of biomarkers are needed to imitate both short- and long-term exposures. Multiple biomarkers at a sub-clinical level represent various elements of disease pathways (Suhaimi & Jalaludin, 2015), and some of these are discussed below.

2.6.1 Blood pressure

In recent years, a growing epidemiological and experimental literature has explored associations between air pollution and BP (Giorgini et al., 2016). Elevated BP or hypertension is an established risk factor for CV events and conditions such as heart disease and stroke. BP is also an important marker of cardiovascular health however, the relationship between air pollution exposure and BP is still not well understood (Schwartz et al., 2012). Additionally, limited studies have explored temporal hemodynamic effects of air pollution through continuous 24-hour ambulatory BP monitoring (ABPM) (Giorgini et al., 2016).

Hypertension is a highly prevalent and well-established cardiovascular risk factor, and observations of BP in relatively asymptomatic individuals has been linked to future CV risk (Lissner, 2002). In recent research, air pollution, also an established CV risk factor, has been hypothesized as a potential contributing factor in CVD through increasing blood pressure (T. Honda et al., 2018).

In other studies, BP increases high enough to initiate CV events such as strokes, MI and heart failure following ambient air pollution exposures (Auchincloss et al., 2008; R. D. Brook et al., 2011; Robert D. Brook, Alan B. Weder, et al., 2011; Giorgini et al., 2016; T. Honda et al., 2018; A. Ibald-Mulli, Stieber, Wichmann, Koenig, & Peters, 2001; Angela Ibald-Mulli et al., 2004) have been reported, however findings have been inconsistent (Choi et al., 2019; Harrabi, Rondeau, Dartigues, Tessier, & Filleul, 2006; Madsen & Nafstad, 2006). Reductions of only 1-2 mmHg however, have shown to markedly reduce CV risk (Ettehad et al., 2016; National Heart Foundation of Australia, 2016; P. Verdecchia et al., 2010).

2.6.1.1 Clinic versus ambulatory measures of blood pressure

Brachial (upper arm) measurements are most frequently used to assess BP and have become entrenched in routine clinical assessment throughout the developed world. This measurement is the most widely accepted estimation of BP for regulatory bodies (Wilkinson, McEniery, Cockcroft, Roman, & Franklin, 2014). In Australia, classifications of clinic BP levels in adults are provided by the National Heart Foundation. These classification categories are presented in Table 2.2 below.

Table 2. 2 Clinic blood pressure classifications in Australian adults.

Classification category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	<80
Normal	120 - 129	and/or	80 - 84
High-normal	130 - 139	and/or	85 - 89
Mild hypertension	140 - 159	and/or	90 - 99
Moderate hypertension	160 - 179	and/or	100 -109
Severe hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	> 140	and	< 90

Source: National Heart Foundation of Australia (2016)

Whilst brachial (peripheral) BP is universally acknowledged to be an acceptable 'proxy measure', it is well known to be a poor surrogate for aortic (central) pressure, which is consistently reported to be lower when compared to corresponding peripheral pressures (C. McEniery & Cockcroft, 2007; Suleman, Padwal, Hamilton, Senthilselvan, & Alagiakrishnan, 2017; Wilkinson et al., 2014). Additionally, central BP measurements have shown stronger associations with end-organ damage and are considered to be of greater clinical use (C. McEniery & Cockcroft, 2007; Suleman et al., 2017).

Ambulatory BP (ABP) monitoring is a useful and accepted clinical tool for obtaining multiple blood pressure measurements outside clinic measurements where unusual variations in readings are sometimes seen (e.g., 'white-coat hypertension') (SunTech Medical Inc, nd). Theoretically, the more sources of variation that can be accounted for (such as within a clinic visit, over a 24-hour period, circadian changes), the more reliable and accurate the BP profile (National Heart Foundation of Australia, 2016).

Ambulatory measurements are traditionally taken over a continuous 24-hour period, and ABP values for systolic and diastolic readings are on average lower than clinic BP values (Williams et al., 2018). ABP monitoring has also shown to be a more sensitive predictor of CV outcomes than clinic BP measures (Williams et al., 2018).

Australian guideline BP measurements for ABP monitoring over 24-hours, daytime (awake) and nighttime (asleep) periods, are set by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2012) and are comparable to international targets shown in Table 2.3 below.

Table 2. 3 Australian and international guidelines for 24-hour ambulatory blood pressure.

Target blood pressure (systolic/diastolic)				
	Australian[a]	**JNC[b]**	**AHA[c]**	**European[d]**
24-hours, mmHg	< 130/80		130/80	130/80
Daytime, mmHg	< 135/85	135/85		135/85
Nighttime, mmHg	< 120/75	120/75		120/70

[a] - National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2012); [b] - JNC (Joint National Committee): Chobanian et al. (2003); [c] - AHA (American Heart Association): G. T. Pickering et al. (2005); [d] - European: Parati et al. (2014).

2.6.1.2 Component measurements of blood pressure

BP consists of several component measurements which quantify different aspects of CV function. The systolic pressure (SBP; the peak pressure during a cardiac cycle; a high SBP indicates high CV load) and the diastolic pressure (DBP; the minimum arterial pressure during a cardiac cycle) are the most commonly studied and elevations in either can lead to a diagnosis of hypertension due to their proven, adverse long-term CV effects (T. Honda et al., 2018). Both SBP and DBP progressively increase with age, although after age 50, DBP tends to decrease (J. Liao & Farmer, 2014; Mitchell, 2008).

2.6.1.3 Review of the literature

The causes of adverse changes in BP are complex, and have traditionally been linked to genetic factors, lifestyle and diet structure. In more recent years, studies have evaluated the potentially pro-hypertensive effects of exposure to various air pollutants. Findings however, have been inconsistent and mixed (Adar et al., 2018; Auchincloss et al., 2008; R. D. Brook, 2017; R. D. Brook et al., 2011; R. D. Brook et al., 2009; Yuanyuan Cai et al., 2016; Choi et al., 2019; E. K. Cosselman et al., 2012; Dvonch et al., 2009; Ebelt, Wilson, & Brauer, 2005; Giorgini et al., 2016; Harrabi et al., 2006; A. Ibald-Mulli et al., 2001; Angela Ibald-Mulli et al., 2004; L. Liu et al., 2009; Madsen & Nafstad, 2006; J. Q. Sun et al., 2008; Urch et al., 2005; Vieira et al., 2017; Ying et al., 2014; A. Zanobetti et al., 2004)the overall evidence supports that incremental elevations in air pollution and particularly $PM_{2.5}$, can raise BP by approximately 1 – 5 mmHg (R. D. Brook & Rajagopalan, 2009).

Both short- and long-term exposures have been implicated with sub-optimal BP outcomes, although short-term exposures to $PM_{2.5}$ have been associated with immediate elevations in BP (Shaowei Wu et al., 2013) and long-term exposure has been associated with the development of hypertension (T. H. Chen et al., 2014). It is also important to note that given the pervasive nature of both air pollution and hypertension throughout the world, even a modest causal relationship is of vast public health importance (R. D. Brook & Rajagopalan, 2009).

In a recent meta-analysis from 16 countries, Yang and colleagues (2018) described significant associations between long- and short-term exposure to air pollution ($PM_{2.5}$, PM_{10} and NO_2) and higher SBP and DBP. However, effect estimates varied widely in magnitude, individual study findings were inconsistent and large degrees of study heterogeneity limited the possibility of interpretation of the associations (B.-Y. Yang, Qian, et al., 2018).

In the Hercules Study (a sub-cohort of the Cohorte Lausanne study), associations of short-term daily exposure to ambient PM_{10} with daytime BP, nighttime BP, and nocturnal BP dipping in French adults (n = 359) was explored. Study participants were aged 38 – 78 years, and residing in Lausanne, Switzerland, which is considered to have low levels of PM air pollution (PM_{10} level: 23.5 ± 13.6 μg/m^3). Whilst air pollution data was obtained from the local regional monitoring network, this is one of few studies to collect data on BP using ABPM. In adjusted models, a 10 μg/m^3 increase in PM_{10} was not significantly associated with daytime SBP, however a 1.32 mmHg (95% CI: 0.06, 2.58 mmHg; p = 0.04) higher nighttime SBP was observed when average concentrations of PM_{10} were used from the same day as the clinical examination (lag 0). A similar result was shown with nighttime SBP when averaged PM_{10} concentrations from one day prior (lag 1) (1.23 mmHg; 95% CI: 0.02, 2.44 mmHg; p = 0.046) were used although effect sizes decreased rapidly with increasing lag days (0 - 5). A 10 μg/m^3 increase in PM_{10} was significantly and positively associated with a 0.72 mmHg higher nighttime DBP at 2 days prior (95% CI: 0.03, 1.42 mmHg; p = 0.042). No significant relationships were reported between 24-hour SBP with PM_{10}, and results were not reported for the association with 24-hour DBP (D. H. Tsai et al., 2012).

In a further study by D.-H. Tsai et al. (2015), associations of short-term exposure to PM_{10} with SBP and DBP was explored in a population-based study conducted in

Switzerland. Participants were aged between 35 – 75 years and data were taken from the Geneva-based Bus Sante study (n = 5605) (average PM_{10} levels: 22.4 μg/m^3) and from the Lausanne-based CoLaus study (n = 6183) (average PM_{10} levels: 31.7 μg/m^3). PM_{10} data was obtained from fixed monitoring stations and the associations of short-term exposure to PM_{10} analysed on the day of the examination visit and up to 7 days before, with SBP and DBP. After adjusting for potential confounders, for each 10 μg/m^3 increase in 7-day PM_{10} average, SBP increased by 0.490 mmHg (95% CI: 0.056, 0.925) in Geneva and 0.036 mmHg (95% CI: 0.042, 0.561) in Lausanne. None of the DBP results were statistically significant (D.-H. Tsai et al., 2015).

Dvonch et al. (2009) reported a significant relationship between community-level exposure to $PM_{2.5}$ and elevated SBP across 347 adults aged 46 ± 14 years, living in Detroit, USA (mean $PM_{2.5}$ levels: 15.0 ± 8.2 μg/m^3). In this study, fixed monitoring site data was used to characterize $PM_{2.5}$ exposure, and BP was defined as an average measure obtained using an automated cuff (non-ambulatory). $PM_{2.5}$ was found to be significantly associated with SBP. Specifically, a 10 μg/m^3 increase in daily $PM_{2.5}$ was associated with a 3.2 mmHg increase in SBP (no 95% CI reported; p = 0.05). No effect was shown on DBP (Dvonch et al., 2009).

Similar results were demonstrated in the US Multi-Ethnic Study of Atherosclerosis (MESA-Air) study where no effect was observed on DBP following exposure to $PM_{2.5}$. In this cross-sectional study of 5112 adults (aged 45 – 84 years) with no previous history of CVD, associations between short-term ambient $PM_{2.5}$ exposures with systolic and diastolic BP were investigated. Data obtained from fixed ambient monitoring sites were used to estimate mean ambient $PM_{2.5}$ (mean $PM_{2.5}$ levels: 16.8 ± 5.0 μg/m^3) exposure for various exposure periods (1, 2, 7, 30 and 60 days), and resting seated BP was measured using a non-ambulatory automated device (Auchincloss et al., 2008). In adjusted models for exposures one to two days prior, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.99 mmHg higher SBP (95% CI: -0.15, 2.13) (Auchincloss et al., 2008).

In a follow-up MESA study by Adar et al. (2018), associations of long- and short-term $PM_{2.5}$ (annual average: 17 μg/m^3) and NO_2 (annual average: 22 ppb) concentrations with systolic and diastolic BP were explored in 6814 participants. In models which adjusted for more traditional CV risk factors (such as BMI, waist-hip ratio, sodium

consumption, diabetes etc.), higher $PM_{2.5}$ and NO_2 concentrations were associated with higher BP levels. These associations increased with larger averaging periods such that an IQR-higher annual average $PM_{2.5}$ concentration (3.1 μg/m^3) was associated with 1.0 mmHg (95%CI: 0.6, 1.4) and 0.4 mmHg (95%CI: 0.2, 0.6) higher SBP and DBP, respectively. Similarly, an IQR-higher NO_2 concentration (16 ppb) was associated with a 2.7 mmHg (95%CI: 1.5, 4.0) higher SBP and 1.0 mmHg (95%CI: 0.3, 1.6) higher DBP. However, when further adjustments were made for calendar time, these associations were fully eliminated (Adar et al., 2018).

Mixed results were reported in the prospective cohort Sister Study. In this work, associations between $PM_{2.5}$ and NO_2 exposure with BP were investigated in American women aged 35 – 76 years (n = 43 629) using geographic systems information to predict individual pollutant concentrations. In adjusted models, a 10 μg/m^3 increase in $PM_{2.5}$ was found to be associated with a 1.4 mmHg higher SBP (95% CI: 0.6, 2.3; p < 0.001) and no relationship was seen with DBP (0.4 mmHg; 95% CI: -0.2, 1.0; p = 0.15). Similarly, a relationship was not observed between NO_2 (10 ppb increase) and SBP (0.2 mmHg; 95% CI: 0.0, 0.5; p = 0.10), although a 0.2mmHg lower DBP was observed (95% CI: -0.4, 0.0; p = 0.05). In co-pollutant models which included both NO_2 and $PM_{2.5}$, the positive association between $PM_{2.5}$ and DBP became stronger and significant. Specifically, in fully adjusted models, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 1.2 mmHg higher DBP (95% CI: 0.5, 1.9; p = 0.001) (Chan et al., 2015).

Using a different measurement metric for NO_2 (μg/m^3) than most other studies, mixed results were reported by Foraster et al. (2014). In this study, a 1.34 mmHg (95% CI: 0.14, 2.55) higher SBP was associated with a 10 μg/m^3 increase in NO_2 (annual average NO_2 level: 26.6 ± 11.7 μg/m^3) in a large study cohort of 3700 adults (aged 35 – 83 years) in Girona, Spain (the REGICOR study). No association was noted with DBP (Foraster et al., 2014).

In a one-year European (Belgium, Milan and Sweden) panel study involving 20 healthy volunteers aged between 59 – 75 years, associations between exposure to ambient air pollution (PM_{10}, $PM_{2.5}$ and NO_2) with BP were investigated. PM data was collected using estimated concentrations from fixed site monitors and NO_2 data was collected using personal exposure samplers. BP was measured using a non-ambulatory

automated device. No significant associations were observed between ambient pollutants and BP however, in the adjusted model, a 10 μg/m^3 increase in ambient PM_{10} and NO_2 resulted in lower SBP. Similarly, a 5 μg/m^3 increase in $PM_{2.5}$ resulted in a higher SBP and lower DBP (Scheers, Nawrot, Nemery, & Casas, 2018). Whilst these results are in contrast to some of those already reported, this outcome is consistent with the views of Robert D. Brook, Alan B. Weder, et al. (2011) who suggest in their review that little evidence exists to suggest gaseous pollutants such as NO_2 will elevate BP.

In contrast to the findings of the above European study, the Third National Health and Nutrition Examination Survey (NHANES III) of 11 623 American participants (median age: 41 years) reported significantly higher systolic, and significantly lower diastolic BP measurements with exposure to PM_{10}. Using estimated averaged data from ambient air quality monitoring sites for PM_{10} exposure, an IQR increase (11.1 μg/m^3) in PM_{10} was significantly associated with a 0.22 mmHg (95% CI: 0.03, 0.41) higher SBP, and a 0.18 mmHg (95% CI: -0.31, -0.05) lower DBP in fully adjusted models (Shanley et al., 2016).

In contrast to the above studies where pollution levels are considered to be low, the population-based Taiwanese Survey on Prevalence of Hyperglycaemia, Hyperlipidaemia, and Hypertension (TWSHHH) examined associations between air pollutants (PM_{10}, NO_2 and CO), and changes in BP in a general population aged between 16 – 90 years (n = 7578), over a range of exposure periods (1-, 3-, and 5-day averages). Air pollution data was obtained from ambient monitoring stations, and levels of pollution were considered to be high (mean PM_{10} level: 55.3 ± 26.2.μg/m^3; mean NO_2 level: 22.4 ± 10.1 μg/m^3; mean CO level: 0.8 ± 0.5 ppm) in comparison to maximum guideline annual mean values for pollutants set by the WHO (Argacha, Bourdrel, & van de Borne, 2018; Riant et al., 2018; World Health Organisation, 2005). BP was measured using an automated non-ambulatory device and in adjusted models, an IQR (34 μg/m^3) increase in 1-day averaged PM_{10} was associated with a 0.47 mmHg (95% CI: -0.09, 1.02; p < 0.001) elevation in SBP. No relationship was observed between gaseous pollutants and systolic or diastolic BP, or between PM_{10} and DBP (Chuang et al., 2010).

In a further study by Chuang et al., (2011) using data (n = 1023; age range: 54 – 90 years) from the Taiwanese Social Environment and Biomarkers of Aging study, the

relationship between changes in BP and long-term (1-year) exposure to similarly high levels of ambient air pollutants was investigated (mean PM_{10} level: 67.8 ± 33.5 μg/m^3; mean $PM_{2.5}$ level: 35.3 ± 15.9 μg/m^3; mean NO_2 level: 24.5 ± 9.5 μg/m^3; mean CO level: 0.9 ± 0.5 ppm). Ambient air pollution was measured using data from ambient monitoring stations and BP was the average of 2 seated readings using an automated non-ambulatory device. In adjusted models, elevations in both systolic and diastolic BP was observed with an IQR increase in 1-year averaged concentrations of PM_{10} (IQR: 48.0 μg/m^3), $PM_{2.5}$ (IQR: 20.42 μg/m^3), and NO_2 (IQR: 12.8 ppb). SBP and DBP elevations were shown to be in the magnitude of 16.34 mmHg (95% CI: 12.27, 20.42) and 14.87 mmHg (95% CI: 12.73, 17.02) for PM_{10}; 32.08 mmHg (95% CI: 21.57, 42.58) and 31.29 mmHg (95% CI: 25.43, 37.14) for $PM_{2.5}$ and 14.40 mmHg (95% CI: 10.98, 17.82) and 12.43 mmHg (95% CI: 10.63, 14.23) for NO_2 (Chuang, Yan, Chiu, & Cheng, 2011).

In conclusion, inconsistent findings have emerged from research focusing on population-level exposures, with several observational studies providing evidence that exposures to higher daily pollution levels are associated with raised systemic arterial BP (Adar et al., 2018; Auchincloss et al., 2008; R. D. Brook, 2017; R. D. Brook et al., 2011; Dvonch et al., 2009; A. Ibald-Mulli et al., 2001; L. Liu et al., 2009; A. Zanobetti et al., 2004). Other studies have shown mixed associations, inverse associations or no association (Choi et al., 2019; Ebelt et al., 2005; Harrabi et al., 2006; Angela Ibald-Mulli et al., 2004; Madsen & Nafstad, 2006) and in animal and controlled-exposure studies in humans, short-term exposures to air pollution have been shown to increase BP (R. D. Brook et al., 2009; E. K. Cosselman et al., 2012; J. Q. Sun et al., 2008; Urch et al., 2005; Vieira et al., 2017; Ying et al., 2014).

2.6.1.4 Nocturnal dipping and non-dipping

The diurnal BP profile typically includes a fall in BP during sleep which is driven by physical inactivity and which is largely independent of an internal rhythm (Hansen et al., 2011). The classifications of nocturnal dipping/non-dipping was introduced by O'Brien, Sheridan, and O'Malley (1988), and a fall of 10% or more in nighttime BP relative to daytime is considered normal or optimal dipping whilst a fall of less than 10% constitutes non-dipping (O'Flynn et al., 2015; Williams et al., 2018). Such classification appears to have advantages from a clinical standpoint and has been used

in studies to demonstrate target organ damage and cardiovascular morbidity in non-dippers (i.e., those with nocturnal SBP dipping of < 10%) (S.-Y. Chen, Chan, Lin, Hwang, & Su, 2014; Ohkubo et al., 2002; Paolo Verdecchia et al., 2012; Viera et al., 2012).

Few studies have examined the relationship between air pollution exposure and nocturnal dipping/non-dipping. However, in a sub-cohort of the Cohorte Lausanne study (the Hercules Study), associations of short-term daily exposure to PM_{10} with daytime BP, nighttime BP, and BP dipping was investigated in 359 adults (aged 38 – 78 years) residing in Lausanne, Switzerland. This study found that after controlling for potential confounders, a 10 $\mu g/m^3$ increase in PM_{10} was associated with a 0.96 mmHg drop in nighttime SBP (95% CI: -1.89, -0.03; $p = 0.044$), however the association was only observed with exposure on the same day. These effect estimates slightly decreased for exposures of 1 – 4 days previously and disappeared from day 5 onwards. No association was observed between PM_{10} exposure and nighttime DBP dipping (D. H. Tsai et al., 2012).

2.6.2 Hemodynamic indices

In addition to maximum and minimum measurements, BP is further composed of steady components (quantified by mean arterial pressure; MAP) and pulsatile components (quantified by pulse pressure; PP) which describe the CV function between BP peaks and troughs of the central aortic pressure wave form (Figure 2.6) (T. Honda et al., 2018; Mitchell et al., 2010). Physiologically, MAP is a surrogate measure for tissue and organ perfusion pressure (J. Liao & Farmer, 2014) and increases modestly with age before age 60 (Mitchell, 2008). PP is considered to be reflective of the pulsatile nature of the transmitted cardiac output and is measured as the difference between SBP and DBP (J. Liao & Farmer, 2014). PP is a surrogate marker for arterial stiffness, and increased PP has been associated with an increased incidence of CV morbidity (J. Liao & Farmer, 2014).

Although rises in PP can be seen due to the aging process and related changes in SBP and DBP (J. Liao & Farmer, 2014), importantly, increases in any or all of these BP components are indicators of vascular disease, and independently predict CV events

and mortality (T. Honda et al., 2018; J. Liao & Farmer, 2014; Vlachopoulos et al., 2010).

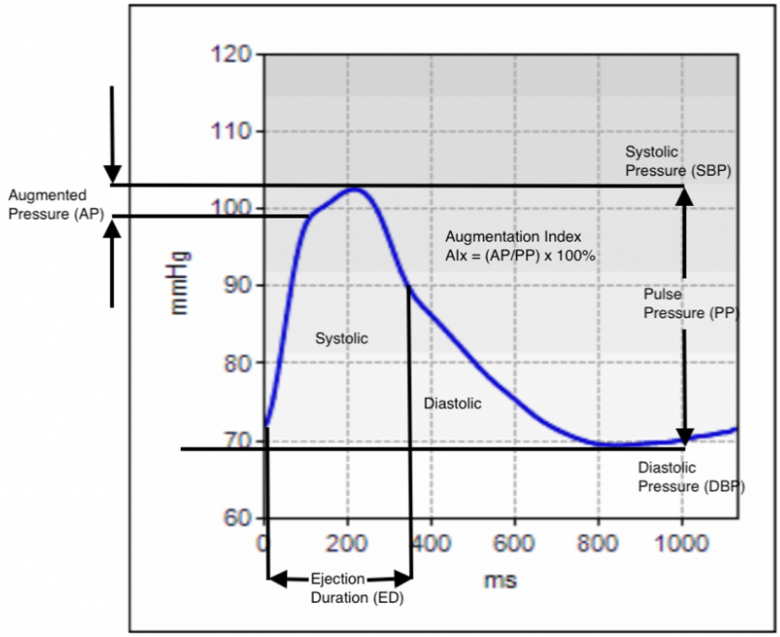

Figure 2. 6 *Representation of a central aortic pressure waveform.*

2.6.2.1 Review of the literature

In the American Heart Association's scientific statement, Brook and colleagues (2010) proposed that ambient air pollutants can adversely affect systemic hemodynamics in healthy individuals (R. D. Brook et al., 2010).

In studies of short-term air pollution exposure, variations in BP have frequently been used as an indicator to evaluate the effects of pollutants on hemodynamic changes however, because of inconsistency among the reported results, the effects on BP remains unclear (R. D. Brook & Rajagopalan, 2009) and data is limited (S.-Y. Chen et al., 2014). Rapid variability in BP on a short-term basis has been proposed to be an important factor contributing to the inconsistent finding of previous studies involving only a single BP measurement (R. D. Brook et al., 2010), as short-term BP variation in response to air pollution exposure is a complicated physiological response tightly regulated by numerous cardiac and vascular homeostatic mechanisms.

In the cross-sectional MESA-Air study, associations between ambient $PM_{2.5}$ with MAP and PP were investigated in 5112 American adults aged 45 – 84 years with no previous history of CVD. Estimated $PM_{2.5}$ exposure data was obtained from fixed monitoring sites for various exposure periods (1, 2, 7, 30 and 60 days). Resting seated BP was measured using an automated device and BP measurements were used to calculate MAP and PP separately (Auchincloss et al., 2008). Whilst no effect was observed with MAP, small effects were shown with PP using the 30-day mean $PM_{2.5}$ exposure (mean $PM_{2.5}$ levels: 16.8 ± 5.0 μg/m^3). Specifically, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with elevations of 1.12 mmHg in PP (95% CI: 0.28, 1.97) in fully adjusted models (Auchincloss et al., 2008).

In the Sister Study described previously, 10 μg/m^3 increases in $PM_{2.5}$ was shown to be associated with a 1.0 mmHg higher PP (95% CI: 0.4, 1.7; $p = 0.001$), and a 0.8 mmHg higher MAP (95% CI: 0.2, 1.4; $p = 0.01$) in fully adjusted models. Similarly, a 10 ppb increase in NO_2 was associated with a 0.4 mmHg (95% CI: 0.2, 0.6; $p < 0.001$) higher PP with no effect shown in MAP (95% CI: -0.2, 0.1; $p = 0.63$). In co-pollutant models which included both NO_2 and $PM_{2.5}$, the association between $PM_{2.5}$ and PP became essentially null and insignificant. Specifically, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.4 mmHg higher PP (95% CI: -0.4, 1.2; $p = 0.30$). However, the association between NO_2 and MAP became stronger and statistically significant with a 10 ppb increase in NO_2 resulting in a 0.3 mmHg lower MAP (95% CI: -0.5, -0.1; $p = 0.02$) (Chan et al., 2015).

Using data from the US Framingham Heart Study Offspring and Third Generation cohorts, Ljungman et al. (2018) reported no association among 5842 participants aged 51 ± 16 years, between MAP with long-term $PM_{2.5}$ exposure (IQR increases; 1.46 μg/m^3), or short-term levels per 5 μg/m^3 increase in $PM_{2.5,}$ 15 000 particles/cm^3 increases in UFP or 0.01 ppm increases in NO_2. Measurements of MAP were obtained using similar technology to the current study. Long-term concentrations of $PM_{2.5}$ were obtained from a spatiotemporal model using satellite-derived data and short-term levels of $PM_{2.5}$, UFP numbers and NO_2 were gathered from fixed monitoring stations.

In the large US NHANES III study of 11 623 adult participants (median age: 41 years), the relationship between PM_{10} exposure with PP (calculated as the difference between SBP and DBP from a set of three measurements taken within the home and then

averaged) was investigated. PM_{10} exposure was estimated using averaged data from ambient air quality monitoring sites. In fully adjusted models, an IQR increase (11.1 $\mu g/m^3$) in PM_{10} was significantly associated with 0.79 mmHg higher PP (95% CI: 0.14, 1.44) (Shanley et al., 2016).

In a Swiss population-based study by D.-H. Tsai et al. (2015), associations of short-term exposure to PM_{10} with PP (calculated as the difference between SBP and DBP) was explored. Participants were aged between aged 35 – 75 years and data were taken from the Geneva-based Bus Sante study (n = 5605) (average PM_{10} levels: 22.4 $\mu g/m^3$), and the Lausanne-based CoLaus study (n = 6183) (average PM_{10} levels: 31.7 $\mu g/m^3$). PM_{10} data was obtained from fixed monitoring stations and the associations of short-term exposure to PM_{10} analysed on the day of the examination visit and up to 7 days before, with PP. After adjusting for potential confounders, for each 10 $\mu g/m^3$ increase in the 7-day PM_{10} average, PP increased by 0.583 mmHg (95% CI: 0.296, 0.870) in Geneva study subjects and 0.183 mmHg (95% CI: 0.017, 0.348) in Lausanne study subjects (D.-H. Tsai et al., 2015).

Dvonch and colleagues (2009) also reported of elevations in PP with increasing levels of ambient $PM_{2.5}$. In this study of 347 adults living in Detroit, USA, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was significantly associated with an increase in PP (4.16 mmHg; p = 0.01, 95% CI not reported) (Dvonch et al., 2009).

In a cross-sectional Greek study conducted by Adamopoulos and colleagues (2010), the relationship between peripheral and central hemodynamics, arterial stiffness and ambient PM_{10} exposure was investigated. In this cohort (n = 1222) of hypertensive patients and normotensive controls, PM_{10} exposure was estimated using data from fixed-site monitors. Positive independent associations were shown between 24-hour mean PM_{10} concentrations with AP (2.0 mmHg per 43.4 $\mu g/m^3$ increase; 95% CI: 0.56, 3.39) and PP (2.78 mmHg per 43.4 $\mu g/m^3$ increase; 95% CI: 3.91, 5.12) denoting a significant effect of PM_{10} concentration on arterial wave reflection magnitude (Adamopoulos et al., 2010).

In a more recent study conducted in Taipei, Taiwan where mean pollution levels are known to be higher than many maximum guideline annual mean values for pollutants set by the WHO (Riant et al., 2018; World Health Organisation, 2005), Chen and colleagues (2014) investigated the difference between the effects of short-term

exposure to $PM_{2.5}$ with BP and hemodynamic changes in 202 adults. Although $PM_{2.5}$ exposure was estimated using data from fixed-site air monitoring sites, this is one of few studies to measure BP using ABPM over a continuous 24-hour period. In adjusted models, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.0 mmHg PP decrease (95% CI: 0.2, 1.8) in individuals with a nocturnal SBP of < 10% ('non-dippers'), however no association was observed in 'dippers' (individuals having SBP of ≥ 10%) (S.-Y. Chen et al., 2014). These results are consistent with an earlier 30-year prospective study undertaken by Chen and colleagues (2012) where short-term exposure to air pollution (PM_{10}, SO_2, NO_2 , CO, ozone) was shown to reduce PP (S.-Y. Chen, Su, Lin, & Chan, 2012).

In conclusion, whilst studies of exposure to various airborne pollutants have demonstrated impacts to the cardiovascular system by altering central hemodynamic parameters, findings have been inconsistent, and effects remain unclear.

2.6.3 Arterial stiffness

Arterial stiffness is another well-recognized modifiable marker of vascular aging and is an independent predictor of adverse CV outcomes across a range of populations (Mitchell et al., 2010; Roman et al., 2007). Arterial stiffening describes a process whereby the arterial system loses compliance and progressive stiffening occurs (J. Liao & Farmer, 2014; Mehta et al., 2014) and has been hypothesized to be affected by short-term exposure to PM (Mehta et al., 2014). Pulse wave velocity (PWV) is the 'gold-standard' for measuring large elastic artery stiffness and is an independent predictor of CV events in middle-aged and older adults with no history of CVD (Clark et al., 2019; Jablonski et al., 2015; Mehta et al., 2014; Mitchell et al., 2010; Townsend et al., 2015; Unosson et al., 2013; Van Bortel et al., 2012; Williams et al., 2018; Zanoli et al., 2017). PWV represents the speed at which the pulse wave travels between two arterial sites (i.e., between the carotid and femoral artery sites) (Figure 2.7) with a higher PWV indicating greater stiffness (Clark et al., 2019). Stiffer vessels are defined by faster transmission times, and a PWV of < 10 m/s is considered optimal (J. Liao & Farmer, 2014; Williams et al., 2018).

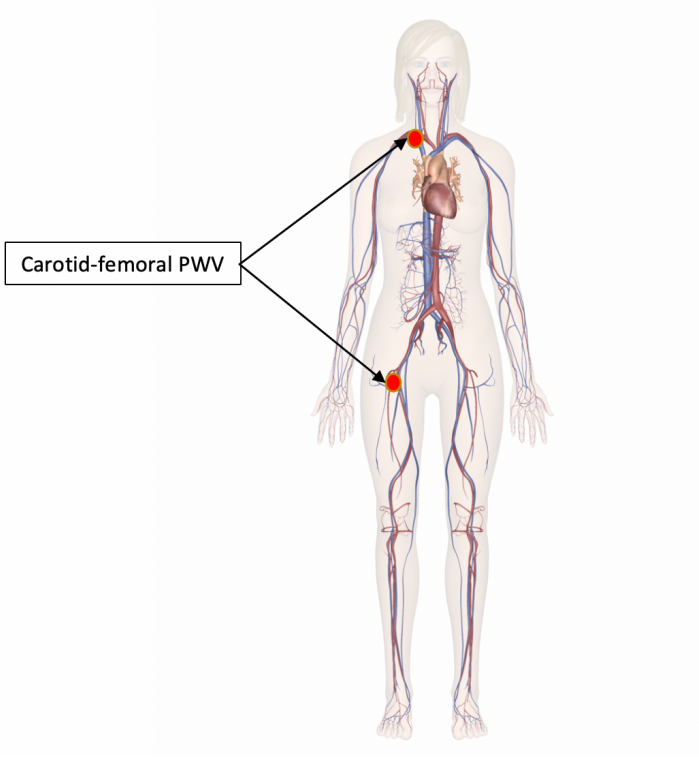

Figure 2. 7 *Measurement sites of carotid-femoral pulse wave velocity.*

A correlate of arterial stiffness and measure of pulse wave reflection, the augmentation index (AIx), is also associated with CVD (Mehta et al., 2014). The central aortic wave form (Figure 2.6) is composed of a forward travelling wave generated during systole (when blood is pumped from the heart) and a later-arriving second pressure wave travelling in the opposite direction which is reflected from the peripheral vessels back into the central circulation (J. Liao & Farmer, 2014; Weber et al., 2004). As arterial stiffness increases, so does transmission velocity of both the forward (incident wave) and backward reflected waves (Weber et al., 2004). This in turn causes the reflected wave from the lower body to arrive sooner in the central aorta and a secondary increase or augmentation of pressure in late systole (Figure 2.8).

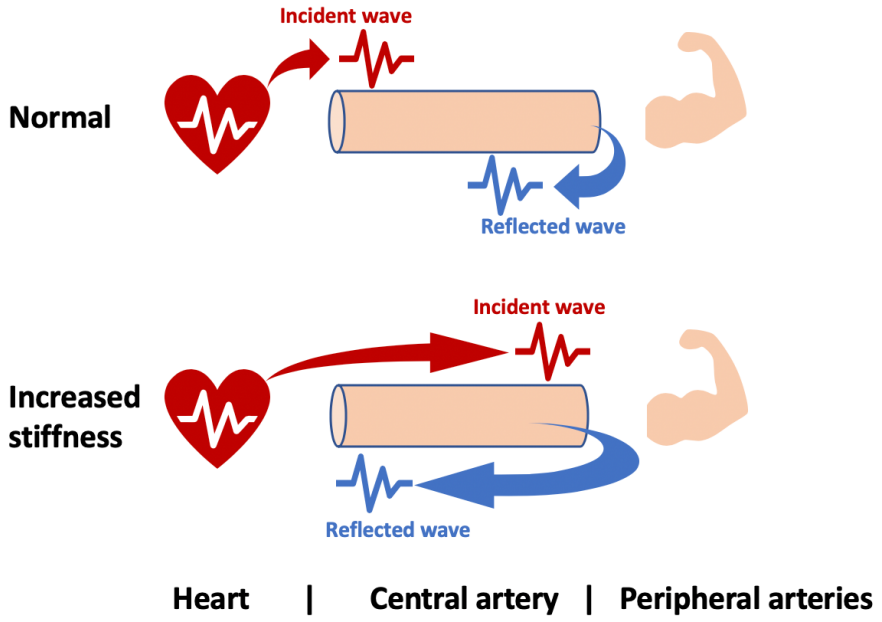

Figure 2. 8 *Schema of transmission of the incident pulse wave and reflected pulse wave in the arterial tree.*

The AIx can be expressed in absolute terms as the ratio of the augmented pressure (AP) to pulse pressure (PP) and represents the merger of forward and backward travelling waves in the central aorta (Suleman et al., 2017). It is presented as a percentage (AIx = [AP / PP] x 100) (J. Liao & Farmer, 2014; Mehta et al., 2014) and larger values of AIx indicate a higher PWV and earlier return of the reflected wave (Mehta et al., 2014). This is caused by stiffer arteries and carries higher risk of organ damage (Mehta et al., 2014). In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx_{75}) is frequently used (Mehta et al., 2014).

Both PWV and AIx (which are measures of arterial stiffness) are vascular biomarkers and sub-clinical predictors for CVD (Zanoli et al., 2017) which reflect functional and structural arterial characteristics (Lenters et al., 2010). Although correlated, PWV and AIx are two different measurements of the properties of the arterial tree that cannot be used interchangeably (Janner, Godtfredsen, Ladelund, Vestbo, & Prescott, 2010; Laurent et al., 2006; O'Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2002).

2.6.3.1 Review of the literature

Studies investigating the relationship between air pollution exposure with measures of arterial stiffness are limited, however it has been hypothesised that exposure to various air pollutants may be associated with adverse physiological responses that might trigger systemic vascular dysfunction and increased BP (Adamopoulos et al., 2010; J. Baumgartner et al., 2018; R. D. Brook et al., 2010; Lenters et al., 2010; Ljungman et al., 2018; Mehta et al., 2014; Scheers et al., 2018; Vlachopoulos et al., 2010; C.-F. Wu et al., 2016).Using data from the Atherosclerosis Risk in Young Adults study, Lenters and colleagues (2010) examined associations between ambient air pollutants ($PM_{2.5}$, NO_2) and established markers of vascular damage including PWV and AIx, in a cohort of young adults (*n* = 750; mean age: 28.4 years) with inherently low cardiovascular risk profiles. Air pollution exposure was estimated using home address geocoding, and PWV and AIx data was collected using the same SphygmaCor technology as the present study. In the fully adjusted model, with the addition of possible intermediate covariates (such as hypertension, HDL, LDL and family history of CVD), a 25 $\mu g/m^3$ increase in NO_2 was associated with a 4.05% higher PWV (95% CI: 0.13, 7.97), and a 37.58% higher AIx (95% CI: 2.23, 72.92). Long-term $PM_{2.5}$ exposure (mean: 21.4 ± 1.1 $\mu g/m^3$) was not associated with either PWV or AIx (Lenters et al., 2010).

In a large cross-sectional community-based project in Greece, with a study population of hypertensive participants and normotensive controls (*n* = 1222), no association was observed between PM_{10} exposure averaged over 5 days (per 43.4 $\mu g/m^3$ increase) with either AIx, AIx_{75} or PWV. Similarly, no association was observed between NO_2 exposure and any outcome measures related to arterial stiffness (PWV, AIx, AIx_{75}) (Adamopoulos et al., 2010; Vlachopoulos et al., 2010).

Scheers et al. (2018) undertook a one-year panel study involving 20 healthy European participants aged between 59 – 75 years and investigated associations between ambient air pollution exposure (PM_{10}, $PM_{2.5}$ and NO_2), with PP and PWV. Data on ambient concentrations of PM_{10} and $PM_{2.5}$ was collected using estimated concentrations from fixed site monitors, and personal exposure to NO_2 data was collected using personal exposure samplers. BP was measured using an automated device (non-ambulatory) and PP was calculated as the difference between SBP and DBP. No significant associations were observed between ambient pollutants and PP however, in the adjusted model, a

10 μg/m^3 increase in PM_{10}, and a 5 μg/m^3 increase in $PM_{2.5}$, resulted in higher PP. Although a relationship was not observed between NO_2 and PP, a 10 μg/m^3 increase in ambient and personal NO_2 concentrations resulted in a higher and lower PP, respectively (Scheers et al., 2018). Conversely, a significant association was observed between a 10 μg/m^3 increase in PM_{10}, and a 5 μg/m^3 increase in $PM_{2.5}$, which resulted in a 2.3 m/s (95% CI: 0.80, 3.47 m/s) and 0.96 m/s (95% CI: 0.32, 1.59 m/s) higher PWV, respectively. No relationship was demonstrated between ambient or personal NO_2 exposure and PWV (Scheers et al., 2018).

In the US Veterans Affairs Normative Aging Study, associations between exposure to air pollutants $PM_{2.5}$ (24-hour mean concentration: 8.6 ± 4.7 μg/m^3) and NO_2 (24-hour mean concentration: 0.02 ± 0.01 ppm), with AIx and AP was investigated in a cohort of elderly men (n = 370; mean age: 78 years; SD: 6.2). In this study, AIx and AP was associated with short-term changes in air pollution using several moving averages of air pollution exposure (4-hours and 1-, 3-, 7- and 14 days) with findings supporting the hypothesis that exposure to air pollution might adversely affect vascular function. Using air quality data from central monitoring sites, it was found that an IQR increase in short-term (3-day) $PM_{2.5}$ exposure (3.6 μg/m^3) was associated with a 0.8% (95% CI: 0.2, 1.4) higher AIx, with similar findings for AP. No association was observed between NO_2 and AIx (Mehta et al., 2014).

Using data from the community-based US Framingham Heart Study Offspring and Third Generation cohorts, Ljungman et al. (2018) reported no association among 5842 participants aged 51 ± 16 years, between measures of arterial stiffness including PWV and AIx with long- or short-term levels of $PM_{2.5}$ or UFP. These authors reported unexpected associations however, between NO_2 and lower arterial stiffness. Measures of arterial stiffness included carotid-femoral PWV and AIx and were carried out using similar technology to the current study. Long-term concentrations of $PM_{2.5}$ were obtained from a spatiotemporal model using satellite-derived data and short-term levels of $PM_{2.5}$, UFP numbers and NO_2 were gathered from fixed monitoring stations.

In a Taiwanese prospective panel study of 89 healthy subjects, significant relationships were shown between $PM_{2.5}$ and brachial-ankle PWV. To reduce the likelihood of exposure misclassification and potentially biased health risk results noted with the use of averaged data from fixed monitoring sites, exposure to $PM_{2.5}$ was assigned using

land use regression estimates combined with indoor monitoring data at the workplace of the participant. In this study, C.-F. Wu et al. (2016) observed 10 μg/m^3 increases in $PM_{2.5}$ to be positively associated with a 2.4% (95% CI: 0.8, 4.0) higher (brachial-ankle) PWV at a one-day lag of exposure. No association was observed between NO_2 with PWV (C.-F. Wu et al., 2016).

Whilst some studies have found that ambient air pollution exposure is associated with sub-optimal changes in metrics of arterial stiffness such as PWV and AIx, these studies are few (Lenters et al., 2010; Mehta et al., 2014). Moreover, findings have been mixed, and the mechanisms responsible for air pollution-mediated increases in large artery stiffness remain unknown (Scheers et al., 2018; Zanoli et al., 2017).

2.6.4 Lipid profile

Serum (or blood) cholesterols (also known as lipids) are fatty substances that are produced by the liver and are carried by the blood to supply material for cell walls and hormones (Australian Institute of Health and Welfare, 2015). Serum cholesterols are composed of several components which have established associations with CVD (Mao et al., 2020), that have been used to predict cardiac risk (Navab M, Reddy S.T., Van Lenten B.J., & A.M., 2011). Although the term 'cholesterol' is commonly used, it actually describes several components circulating in blood.

2.6.4.1 Components of serum cholesterol

Low-density lipoproteins or LDL are able to penetrate the surfaces of arterial walls to form fatty streaks and deposits on arterial walls which can narrow and stiffen the vessel (atherosclerosis). LDL is a well-established mediator of CVD pathogenesis and progression (McGuinn et al., 2019) and elevated levels are known to trigger adverse CV events such as heart attacks and stroke. A low LDL level is considered optimal for CV health (Carrington & Stewart, 2011; National Heart Foundation of Australia, nd; X. M. Wu et al., 2019).

In contrast, high-density lipoproteins (HDL) or 'good' cholesterol transports excess cholesterol from cells back to the liver for processing or excretion, and thus may reduce atherosclerotic plaques and the subsequent risk of heart attack or stroke (Carrington & Stewart, 2011; National Heart Foundation of Australia, nd).

Triglycerides (TG) are the chemical form in which most fats exist. They have a role in metabolism as an energy source and assist in the transfer of dietary fat throughout the body. High levels can contribute to fatty plaques in blood vessels (Australian Institute of Health and Welfare, 2015) and have been identified as a risk factor for CVD (J. M. Miller et al., 2011).

Total cholesterol (TC) is a composite of different lipid measurements and is calculated by adding together LDL and HDL levels plus 20% of the triglyceride level. Dyslipidemia (elevated TG, LDL or TC, lowered HDL) and metabolic syndrome increase the risk of CVD and T2DM (International Diabetes Federation, 2006; Mao et al., 2020; Sarah Rajkumar et al., 2019)

Australian guidelines for serum cholesterols are provided by the Royal Australian College of General Practitioners (RACGP) and are shown at Table 2.4.

Table 2. 4 Australian guidelines for cholesterol and other lipids.

Lipid	Guideline
Total cholesterol	< 4.0 mmol/L
High-density lipoprotein	≥ 1.0 mmol/L
Low-density lipoprotein	< 2.0 mmol/L
non-HDL	< 2.5 mmol/L
Triglycerides	< 2.0 mmol/L

Source: Royal Australian College of General Practitioners (2019).

2.6.4.2 Review of the literature

Despite that a causal association between air pollution (mostly PM) and adverse health outcomes, possibly involving dyslipidemia, have been reported (Yitshak Sade, Kloog, Liberty, Schwartz, & Novack, 2016), few studies have explored links between air pollution exposure with blood lipid levels (D. G. Bell et al., 2017; H. H. Chen et al., 2020; Mao et al., 2020; Yitshak Sade et al., 2016; K. Zhang et al., 2021; X.-Y. Zhang et al., 2020).

In a 10-year (2003 – 2012), population-based retrospective cohort study (n = 73 117) in Southern Israel, Yitshak Sade et al. (2016) examined associations between PM (PM_{10}, $PM_{2.5}$) with lipids (TG, HDL, LDL). The study population was comprised of

adult participants who were smokers, or had been diagnosed with a cardiovascular (e.g., stroke, hypertension, dyslipidemia etc) or metabolic condition (e.g., diabetes). PM_{10} and $PM_{2.5}$ exposure was estimated using a satellite-based model over three exposure periods: 1-, 2- to 3-day and 1-week moving average concentrations. In adjusted models and using IQR increases in concentrations of PM_{10} and $PM_{2.5}$, negligible or no association was observed between acute exposures to PM_{10} (1-day before blood test) with LDL (0.03%; 95% CI: 0.01%, 0.06%), triglycerides (0.00%; 95% CI: -0.04%, 0.03%), and HDL (-0.01%; 95% CI: -0.02%, 0.00%). The associations observed with $PM_{2.5}$ over 2-, 3-day and 1-week average concentrations of the pollutants were similar (no quantitative results reported) (Yitshak Sade et al., 2016). When assessing the effect of intermediate exposures over a 3-month averaging period, significant associations were observed with modest elevations in LDL (PM_{10}: 2.32%; 95% CI: 2.15%, 2.49%; $PM_{2.5}$: 1.42%; 95% CI: 1.23%, 1.60%), TG (PM_{10}: 0.23%; 95% CI: 0.02%, 0.42%; $PM_{2.5}$: 0.37%; 95% CI: 0.14%, 0.59%) and reductions in HDL (PM_{10}: 1.13%; 95% CI: -1.23%, -1.03%; $PM_{2.5}$: 1.30%; 95% CI: -1.40%, -1.19%). In a stratified analyses, among participants without diabetes, IQR increases in 3-month average concentrations of PM_{10} and $PM_{2.5}$ were similarly associated to that of the unstratified analyses for LDL (Yitshak Sade et al., 2016).

In the MESA-Air, associations between long- and short-term exposures to concentrations of $PM_{2.5}$ (averaging exposure periods of 12 months, 3 months and 2 weeks) with HDL in a healthy cohort of 6654 adults was tested. Using predicted individually weighted $PM_{2.5}$ concentrations in a minimally adjusted model, significant associations were reported between a 5 $\mu g/m^3$ increase in $PM_{2.5}$ and reductions in HDL (-0.86 mg/dL, 95% CI: -1.38, -0.34), over a 2-week averaging period. However, this association diminished after adjusting for further covariates (-0.39 mg/dL, 95% CI: -0.97, 0.18). No significant associations were found between annual and intermediate (3-month averaging period) $PM_{2.5}$ exposure with HDL (D. G. Bell et al., 2017).

In very recent work by J. S. Kim et al. (2019), associations of short-term (prior 1-month) and long-term (prior 1-year) ambient air pollution exposures (including PM_{10}, $PM_{2.5}$ and NO_2) were examined with various indicators of cardiometabolic health (including TG, TC, HDL and LDL) in a cohort of young adults (n = 158) aged 17- 22 years. In this study, the Metabolic and Asthma Incidence Research study (Meta-AIR), air quality data was obtained from ambient monitoring stations, and exposure was recorded using

averaged air pollution data for prior 1-month and 1-year to reflect short- and long-term exposure. In adjusted models, a one standard deviation (SD) change in long-term (1-year) NO_2 exposure was significantly associated with 11.25 mg/dL higher total cholesterol (p = 0.04) and 9.37 mg/dL higher LDL cholesterol (p = 0.04). No relationship was observed between NO_2 with TG and HDL. Exposure to elevated concentrations of both PM_{10} and $PM_{2.5}$ showed non-significant elevations in all lipid measures other than $PM_{2.5}$ with HDL, which showed a decrease. Whilst elevations in levels of TG, TC, HDL and LDL were observed with a SD increase in short-term (1-month) exposure to NO_2, PM_{10} and $PM_{2.5}$, these relationships were not significant. A similar inverse relationship was also shown between PM_{10} with LDL (J. S. Kim et al., 2019).

In other very recent work using longitudinal data from the US Study of Women's Health Across the Nation (SWAN), similar results to other studies was demonstrated. This study followed a large midlife cohort (n = 2289) of women aged 42 – 52 years and examined associations between average exposure to ambient $PM_{2.5}$ and gaseous co-pollutants with blood lipids. Estimated averages of $PM_{2.5}$ and gaseous co-pollutants were obtained from ambient monitoring data and assigned to each participant from geocoded addresses using retrospective exposure periods of 1-year (long-term), 30 days (medium term) and 1-day (short-term). In adjusted mixed-effect models, $PM_{2.5}$ exposure was negatively associated with HDL, and positively associated with TC. Specifically, each 3 $\mu g/m^3$ increase of 1-year $PM_{2.5}$ exposure was associated with a decrease of 0.7% (95% CI: -1.40%, -0.10%; $p < 0.05$) in protective HDL cholesterol. For intermediate exposure (30-day), a 5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 0.3% higher TC (95% CI: -0.01, -0.60; $p < 0.1$). No associations were observed between any time period of exposure (1- year, 30 days or 1-day) to $PM_{2.5}$ with LDL or TG (X. M. Wu et al., 2019).

In the large NHANES III conducted in the US, associations between PM_{10} levels with circulating lipids including TG, TC, HDL and LDL was investigated in 11 623 adult participants (median age: 41 years). Average exposure for PM_{10} at the residences of participants was estimated based on averaged data from ambient air quality monitoring sites. In fully adjusted models, an IQR increase in PM_{10} (11.1 $\mu g/m^3$) was significantly associated with higher levels of TG (2.42 mg/dL; 95% CI: 1.09, 3.76), TC (1.43 mg/dL; 95% CI: 1.21, 1.66) and LDL (1.81 mg/dL; 95% CI: 0.81, 1.56), and lower levels of

HDL (0.18 mg/dL; 95% CI: - 0.32, 0.68), although the later was not statistically significant (Shanley et al., 2016).

Using pooled data from two large European cohorts (the HUNT and Lifelines studies) (n = 144 082), the relationship between ambient air pollution and blood lipids including TC, TG and HDL was tested. Exposure to air pollutants PM_{10} and NO_2 was estimated using land use regression models attached to a participant's recruitment address. The findings of this study showed that in adjusted models (all models also included adjustment for noise) an IQR increase in PM_{10} (2 μg/m^3) and NO_2 (7.4 μg/m^3) was associated with elevations in TG of 1.9% (95% CI: 1.5, 2.4%) and 2.2% (95% CI: 1.6, 2.7%), respectively. A similar significant relationship was observed per IQR higher NO_2 exposure with HDL (0.5%; 95% CI: 0.3, 0.8). Non-significant relationships were reported between an IQR increase in PM_{10} and higher HDL levels (0.2%; 95% CI: -0.1, 0.4). No associations were observed between any of the pollutants and TC (Yutong Cai et al., 2017).

It is important to note however that similar mixed results have also been reported in Asian studies where mean pollution levels are known to be significantly higher than many maximum guideline annual mean values for pollutants set by the WHO (Argacha et al., 2018; Lim & Thurston, 2019; Riant et al., 2018; World Health Organisation, 2005).

In the recent 33 Communities Chinese Health Study, Yang et al., (2018) reported significant deleterious associations between 10 μg/m^3 increases in PM_1, $PM_{2.5}$ and NO_2 with higher levels of TC (PM_1: 1.6%; 95% CI: 1.1, 2.0; $PM_{2.5}$: 1.1%; 95% CI: 0.8, 1.4; NO_2: 0.7%; 95% CI: 0.0, 1.4). Similar associations were observed between $PM_{2.5}$, PM_{10} and NO_2 with higher levels of TG ($PM_{2.5}$: 1.1%; 95% CI: 0.4, 1.8; PM_{10}: 4.7%; 95% CI: 3.6, 5.9; NO_2: 6.0%; 95% CI: 3.5, 8.6). Although higher levels of TG were demonstrated with exposure to PM_1, this relationship was not significant (2.9%; 95% CI: -3.3, 9.3). HDL levels were observed to significantly decrease with 10 μg/m^3 increases in PM_1, $PM_{2.5}$ and NO_2 (PM_1: -1.4%; 95% CI: -1.8, -0.9; $PM_{2.5}$: -1.1%; 95% CI: -1.4, -0.8; NO_2: -1.6%; 95% CI: -2.3, -1.0), however the relationship was not significant with PM_{10} (- 0.2%; 95% CI: - 0.7, 0.2). Mixed results were shown with LDL. Significant associations were observed between 10 μg/m^3 increases in PM_1 and $PM_{2.5}$ with higher levels of LDL (PM_1: 3.2%; 95% CI: 2.6, 3.9; $PM_{2.5}$: 2.9%; 95% CI: 2.4,

3.5), although LDL were shown to reduce with exposure to PM_{10} (-0.9%; 95% CI: -1.3, -0.4). A non-significant relationship was demonstrated between 10 μg/m^3 increases in NO_2 and lower LDL levels (-0.1%; 95% CI: -1.2, 1.1) (B.-Y. Yang, Bloom, et al., 2018).

In another study conducted in Taiwan (TWSHHH), Chuang et al. (2010) investigated changes in various cardiometabolic risk factors, including blood lipids in a general population aged between 16 – 90 years (n = 7578), with exposure to ambient air pollution over a range of exposure periods (1-, 3-, and 5-day averages). Daily concentrations of pollutants including PM_{10}, NO_2 and CO were obtained from the nearest fixed-site monitoring station and used to represent each participant's air pollution exposure. In adjusted models, an IQR increase in 1-day averaged PM_{10} predicted an increase in TG of 2.96 mg/dL (95% CI: -0.07, 5.99; $p < 0.10$) and a 0.90 mg/dL (95% CI: -1.46, -0.34; $p < 0.01$) reduction in HDL levels. No relationship was reported between PM_{10} exposure and LDL, although non-significant reductions were shown in LDL levels (1-day: - 0.52 mg/dL; 95% CI: -1.52, 0.47; 3-day: -0.61 mg/dL; 95% CI: -1.73, 0.52; 5-day: -0.84 mg/dL; 95% CI: -1.86, 0.17). No relationship was observed between any lipid markers with NO_2 and CO (Chuang et al., 2010).

In a secondary analysis of data from the Taiwanese Social Environment and Biomarkers of Aging study (n = 1023; age range: 54 – 90 years), Chuang and colleagues (2011) investigated the relationship between 1-year averaged concentrations of air pollutants including PM_{10}, $PM_{2.5}$, NO_2 and CO with TC, TG and HDL. In adjusted models, significant associations were observed between PM_{10}, $PM_{2.5}$ and NO_2 with elevations in TC (PM_{10}: 42.86 mg/dl, 95% CI: 34.59, 51.13; $PM_{2.5}$: 75.39 mg/dl, 95% CI: 54.30, 96.48; NO_2: 39.31 mg/dl, 95% CI: 32.38, 46.24). In contrast, TG and HDL were not associated with any of these pollutants (Chuang et al., 2011).

In conclusion, investigations of associations between various air pollutants and serum lipid levels have yielded mixed results although several epidemiologic studies have shown modest adverse associations using a range of exposure windows, and various metrics for increasing concentrations to attain a β value (most frequently an IQR or nominated unit increase) (D. G. Bell et al., 2017; Yutong Cai et al., 2017; Z. Chen et al., 2016; Chuang et al., 2010; Chuang et al., 2011; Shanley et al., 2016; X. M. Wu et al., 2019; B.-Y. Yang, Bloom, et al., 2018; Yitshak Sade et al., 2016). Positive

associations between elevated levels of ambient air pollutants including PM, NO_2, ozone and black carbon have been reported with total cholesterol (Chuang et al., 2011; Shanley et al., 2016; B.-Y. Yang, Bloom, et al., 2018), triglycerides (Chuang et al., 2010; Shanley et al., 2016; B.-Y. Yang, Bloom, et al., 2018; Yitshak Sade et al., 2016), and LDL (Shanley et al., 2016; B.-Y. Yang, Bloom, et al., 2018; Yitshak Sade et al., 2016), however not all studies have observed effects (Sarah Rajkumar et al., 2019; Xiao et al., 2016). Associations with HDL have also been mixed (Shanley et al., 2016; Xiao et al., 2016; B.-Y. Yang, Bloom, et al., 2018) and few studies have reported on associations with other gaseous pollutants including VOC.

2.6.5 Glucose metabolism

T2DM is a chronic metabolic disorder that is defined by a variety of symptoms based on an agreed glycaemic measure, and across this scale, individuals can be diagnosed with 'prediabetic' conditions including states of impaired fasting glucose or impaired glucose tolerance (Cong Liu et al., 2016; Twigg, Kamp, Davis, Neylon, & Flack, 2007). Although these prediabetic conditions are not diabetes, they are significant risk factors for diabetes and CVD in the future (Cong Liu et al., 2016; Royal Australian College of General Practitioners, 2016; Twigg et al., 2007). In addition to well-established risk factors including physical inactivity, obesity, hypertension and atypical cholesterol and triglyceride levels (Royal Australian College of General Practitioners, 2016), there is increasing evidence indicating that air pollution might also be an important risk factor for T2DM (Balti, Echouffo-Tcheugui, Yako, & Kengne, 2014; Esposito, Petrizzo, Maiorino, Bellastella, & Giugliano, 2015; I. C. Eze et al., 2015; Ikenna C. Eze et al., 2015; Cuiqing Liu, Ying, Harkema, Sun, & Rajagopalan, 2013; S. K. Park & Wang, 2014).

Traditionally, measures for the classification and diagnosis of diabetes have relied on measurements of plasma (or blood or serum) glucose concentrations in planned samples such as fasting glucose or non-fasting samples following metabolic stress tests, or an oral glucose tolerance test (The International Expert Committee, 2009). It is known that chronic hyperglycemia (an excess of glucose in the blood often associated with T2DM) is a hallmark of diabetes and as such, more recently, measures of long-term glycaemic exposure have been suggested as a superior marker for the existence and severity of T2DM, than single measures (The International Expert Committee, 2009).

Glycated hemoglobin or HbA1c, is a method for monitoring glucose metabolism control (Chuang et al., 2010) and is considered to be a reliable measure of chronic glycaemia levels over a longer exposure time (The International Expert Committee, 2009). Elevated HbA1c levels represent an increased risk of developing diabetes and its complications, and in general populations, relationships have been observed between increasing HbA1c and an increased risk of developing hard arterial plaques and CVD (Jørgensen et al., 2004). Furthermore, increases in exposure to PM have been associated with elevations in HbA1c (Chuang et al., 2010).

Included in Table 2.5 is a summary of diagnostic values for both fasting glucose and HbA1c adopted by the RACGP.

Table 2. 5 Fasting glucose and HbA1c diagnostic values for Type 2 diabetes**.**

Fasting glucose		
	Diabetes unlikely	< 5.5 mmol/L
	Diabetes uncertain	5.5 - 6.9 mmol/L
	Diabetes likely	≥ 7.0 mmol/L
HbA1c		≤ 6.5 %

Source: Royal Australian College of General Practitioners (2019).

2.6.5.1 Review of the literature

T2DM is a leading cause of years of life lost, whereas ambient air pollution is a leading risk factor for the global burden of disease in nations with a high sociodemographic index (Forouzanfar et al., 2016; Gakidou et al., 2017; Landrigan, Fuller, Acosta, et al., 2018; Naghavi et al., 2017). An accumulating body of evidence suggests that exposure to air pollution is associated with prevalence and incidence of T2DM (Balti et al., 2014; R. D. Brook, Jerreft, Brook, Bard, & Finkelstein, 2008; Coogan et al., 2012; I. Eze et al., 2014; Trenton Honda et al., 2017; Lim & Thurston, 2019; Cong Liu et al., 2016; Renzi et al., 2018; Weinmayr et al., 2015).

Since the 2010 AHA statement, further evidence has amassed linking air pollution exposure with insulin resistance (R. D. Brook et al., 2010). Insulin resistance is a condition described by decreased tissue sensitivity to the action of insulin. It is an independent predictor for T2DM however is present long before the onset of T2DM

and is often referred to as a pre-diabetic state (S. Lucht et al., 2019; S. A. Lucht et al., 2018; Wolf et al., 2016). The pathway to insulin resistance is unclear and in an effort to clarify these pathways, several epidemiological studies have investigated whether higher air pollution exposure mediates elevated blood glucose levels, a potential sign and pathway to increased insulin resistance and consequently T2DM (S. A. Lucht et al., 2018).

Despite the importance of understanding the connection between air pollution exposure and diabetes, few studies have explored its effects on glucose homeostatic measures such as serum glucose and HbA1c in non-diabetic individuals (Chuang et al., 2010; Cong Liu et al., 2016; S. A. Lucht et al., 2018; Riant et al., 2018).

In an effort to clarify these pathways, several more recent epidemiological studies have explored whether higher air pollution exposure is associated with elevated blood glucose levels and HbA1c (Trenton Honda et al., 2017; Cong Liu et al., 2016; S. A. Lucht et al., 2018; Riant et al., 2018). In attempting to understand these relationships, it is critical to note that whilst serum glucose values can vary widely over a short period of time, HbA1c is a recognized marker that reflects average blood glucose levels over the previous 30 – 120 days and is useful for assessing glucose levels and potential insulin resistance (S. A. Lucht et al., 2018; Riant et al., 2018). Therefore, it has been hypothesized that HbA1c might be a better clinical indicator in studies of a presumed association between T2DM and long-term exposure to air pollution (Riant et al., 2018).

In a 10-year retrospective study in Southern Israel conducted by Yitshak Sade et al. (2016), associations between ambient PM with serum glucose measures were investigated. Adult participants were recruited who were smokers or who suffered a cardiometabolic condition (e.g., history of stroke, hypertension, dyslipidemia, diabetes etc). PM_{10} and $PM_{2.5}$ exposure was estimated using a satellite-based model over three exposure periods: 1-, 2- to 3-day and 1-week moving average concentrations. Using IQR increases in adjusted models, negligible associations were observed between acute exposures to PM_{10} (1-day) and elevations in glucose levels (0.03%; 95% CI: 0.003, 0.057%). In assessing the effect of intermediate-term PM_{10} and $PM_{2.5}$ exposure (3-month average concentration), significant increases in glucose were observed following PM_{10} (0.30%; 95% CI: 0.153, 0.452%) exposure however, not with $PM_{2.5}$ (0.02%; 95% CI: -0.12, 0.18%). In a subsequent stratified analysis by diabetic status, IQR increases

in the 3-month average concentration of PM_{10} and $PM_{2.5}$ was associated with a 0.28% (95% CI: 0.14, 0.42%) rise, and a 0.55% (95% CI: -0.69, - 0.41%) fall in serum glucose, respectively, in non-diabetics (Yitshak Sade et al., 2016).

In the more recent ongoing prospective population-based Heinz Nixdorf Recall study, non-diabetic participants aged 45 – 75 years were recruited from the Ruhr area of Germany. This study examined associations between medium-term air pollution exposures (28-day and 91-day) with blood glucose and HbA1c using estimates of exposure related to residential address. Positive associations were shown in adjusted models between blood glucose levels and an IQR (5.7 $\mu g/m^3$) increase in $PM_{2.5}$ (28-day: 0.91 mg/dL; 95% CI: 0.38, 1.44, 91-day: 0.81 mg/dL; 95% CI: 0.05, 1.58) and 28-day estimates of PM_{10} (28-day: 0.59 mg/dL; 95% CI: 0.04, 1.14). Similar observations were shown between HbA1c with an IQR (4.0 $\mu g/m^3$) increase in both $PM_{2.5}$ (28-day: 0.03%; 95% CI: 0.01, 0.05, 91-day: 0.07%; 95%CI: 0.04, 0.10) and PM_{10} (28-day: 0.04%; 95% CI: 0.02, 0.06, 91-day: 0.04%; 95%CI: 0.02, 0.06). No relationship was observed between NO_2 exposure with blood glucose or with HbA1c (S. A. Lucht et al., 2018).

Again, in a recent study by Riant et al. (2018), associations between exposure to ambient air pollutants NO_2 and PM_{10} with levels of HbA1c and fasting blood glucose in ~ 2500 French adults, aged 40 to 65 was investigated. Levels of air pollution in the study area, Lille and Dunkirk urban areas, are considered to be relatively low but are close to the WHO's maximum guideline values. Air pollution data was estimated using an atmospheric dispersion modelling system which incorporates pollution data related to localized natural and manmade sources, and ambient data from monitoring stations (Riant et al., 2018). Using multivariate analysis, significant associations were demonstrated between HbA1c with both NO_2 and PM_{10}. In fully adjusted models, an increase of 5 $\mu g/m^3$ in NO_2 was associated with a 0.031% (95% CI: 0.010, 0.053; p = 0.005) higher HbA1c. Similarly, an increase of 2 $\mu g/m^3$ in PM_{10} concentration was associated with a 0.045% (95% CI: 0.021, 0.068; p = 0.0002) higher HbA1c. There was a significant association between higher fasting blood glucose (0.0093%; 95% CI: 0.0015, 0.0171; p = 0.02) and a 5 $\mu g/m^3$ increase in PM_{10} in the basic model (adjusted for sex, age, urban area and period of blood sample), however this was diminished in the fully adjusted model (0.0073%; 95% CI: -0.0003, 0.0150; p = 0.06) (adjusted using the same covariates as Model 1 with the addition of BMI, educational level, smoking

status, pack-years, physical activity and season). No relationship was shown between NO_2 with blood glucose (Riant et al., 2018).

In another large study (*n* = 5958; mean age 51 years), conducted in north eastern USA where air pollution levels are also relatively low, associations between ambient air pollution and measures related to glucose homeostasis in healthy middle-aged adults was examined. $PM_{2.5}$ exposure was estimated by a satellite-based model attached to the participant's address, and information related to glucose homeostasis was obtained by using data collected from the Framingham Offspring and Third Generation cohorts (subsets of the Framingham Heart Study). This study examined associations between measures of glucose homeostasis including fasting blood glucose and HbA1c with proximity to major highways, presuming that those who lived closer to major roadways were likely to be exposed to higher and more sustained levels of $PM_{2.5}$. The findings of this study indicate that participants living 64m (25^{th} percentile) from a major highway had a 0.28% (95% CI: 0.05, 0.51) higher fasting blood glucose than participants living 413m (75^{th} percentile) away, and the association appeared to be driven by participants who lived within 50m from a major roadway. No relationship was observed between higher exposures to $PM_{2.5}$ with HbA1c (Li et al., 2018).

In the Meta-AIR study conducted in Southern California, associations of long-term (prior 1-year) and short-term (prior 1-month) ambient air pollution exposures with fasting glucose were investigated in a cohort of young adults (*n* = 158) aged 17- 22 years. Using air quality data from ambient monitoring stations, exposure was recorded using averaged air pollution data for the prior 1-year and 1-month to reflect long- and short-term exposure. Whilst no relationship was shown between long-term exposure to NO_2, PM_{10} and $PM_{2.5}$ with fasting glucose, it was noted that increases in these pollutants resulted in lower fasting glucose. Similarly, no significant relationship was noted between short-term (1-month) exposures to NO_2 or either PM size fraction with fasting glucose however, increases in fasting glucose were shown with exposure to higher levels of NO_2, and decreased with exposure to PM (J. S. Kim et al., 2019).

In the National Social Life, Health, and Aging Project (NSHAP), associations between HbA1c levels with $PM_{2.5}$ and NO_2 were investigated. This is a prospective, population-based study of 4121 older Americans (57 + years) and similar to many other studies, air pollution exposure was estimated using spatiotemporal models and data from the

nearest air quality monitoring station. The findings of this study showed an IQR (8.6 ppb) increase in NO_2 was significantly associated with 0.8% (± 0.2%; $p < 0.01$) higher HbA1c levels. A non-significant relationship was observed between an IQR increase (3.9 μg/m^3) in $PM_{2.5}$ with higher HbA1c (0.2% ± 0.2%) (Trenton Honda et al., 2017).

Using pooled data from two large European cohorts (the HUNT and Lifelines studies) (n = 144 082), associations between fasting blood glucose and HbA1c with ambient air pollution were investigated. Exposure to air pollutants PM_{10} and NO_2 was estimated using land use regression models attached to a participant's recruitment address. The findings of this study showed that in basic adjusted models (adjusted for age, sex) an IQR increase in PM_{10} (2 μg/m^3) and NO_2 (7.4 μg/m^3) was significantly associated with a 0.5% (95% CI: 0.4, 0.7), and 0.5% (95% CI: 0.4, 0.7), higher fasting blood glucose level, respectively. Effects were slightly increased with the addition of further covariates including season of blood draw, smoking status, employment and alcohol status however, effect levels returned to that of the basic model with the further inclusion of co-pollutants including noise. Corresponding associations were not observed with HbA1c (Yutong Cai et al., 2017).

In a study conducted in China, where $PM_{2.5}$ levels are consistently high (WHO annual $PM_{2.5}$ mean value: 10 μg/m^3) (Lim & Thurston, 2019; Riant et al., 2018; World Health Organisation, 2005), Liu and colleagues (2016) reported that an annual average IQR increase (41.1 μg/m^3) in $PM_{2.5}$ (mean ± SD: 72.6 ± 27.3 μg/m^3) was significantly associated with a 0.26 mmol/L (95% CI: 0.19, 0.32) higher fasting glucose level, and a 0.08% (95% CI: 0.06, 0.10) higher HbA1c (Cong Liu et al., 2016).

Similarly, high levels of air pollution are consistently reported in Taiwan and using data from the TWSHHH study (n = 7578), Chuang et al. (2010) investigated associations between measures of glucose metabolism in a general Taiwanese population (aged 16 - 90 years), with exposure to ambient air pollution over a range of exposure periods (1- , 3-, and 5-day averages). Daily concentrations of pollutants including PM_{10}, NO_2 and CO were used to represent each resident's air pollution exposure by assigning each of them to the nearest fixed-site monitoring station. In this study, an IQR increase in 3-day averaged PM_{10} was associated with a 0.06% (95% CI: 0.01, 0.11; $p < 0.01$) higher HbA1c, however non-significant associations were found for other exposure periods (1-day: -0.02%; 95% CI: -0.07, 0.02; 5-day: 0.02%; 95% CI: -0.02, 0.06). Non-

significant associations were also observed between elevated PM_{10} and fasting blood glucose (1-day: -0.44 mg/dL; 95% CI: -1.49, 0.60; 3-day: 0.25 mg/dL; 95% CI: -0.76, 1.27; 5-day: 0.50 mg/dL; 95% CI: -0.38, 1.38), and study results were not reported between glucose metabolism parameters and gaseous pollutants, NO_2 and CO (Chuang et al., 2010).

In a further study by Chuang and colleagues (2011) conducted on 1023 elderly individuals in Taiwan (age range: 54 – 90 years), and using data from the Taiwanese Social Environment and Biomarkers of Aging study, long-term exposure to fine particles (mean concentration ≅ 35 $\mu g/m^3$) was associated with elevations in HbA1c. In adjusted models, significant associations were observed between and IQR increase in 1-year averaged air pollutants PM_{10}, $PM_{2.5}$ and NO_2 with higher fasting glucose (PM_{10}: 22.88 mg/dl, 95% CI: 14.93, 30.82; $PM_{2.5}$: 36.55 mg/dl, 95% CI: 19.20, 53.90; NO_2: 17.03 mg/dl, 95% CI: 10.37, 23.69) and HbA1c (PM_{10}: 1.40%, 95% CI: 1.11, 1.69; $PM_{2.5}$: 2.24%, 95% CI:1.47, 3.00; NO_2: 1.08%, 95% CI: 0.84, 1.33) (Chuang et al., 2011).

In conclusion, while prior studies have linked air pollution to diabetic prevalence and incidence (S. Lucht et al., 2019), data on associations between glucose homeostasis biomarkers and air pollution are scarce (Riant et al., 2018) and remain inconsistent for specific pollutants (e.g., PM, NO_2, VOC) over both short- and long-term exposures (L. Chen et al., 2016; Trenton Honda et al., 2017; Li et al., 2018; Cong Liu et al., 2016; S. A. Lucht et al., 2018; Rajagopalan & Brook, 2012; Wolf et al., 2016).

2.6.6 Renal function

The presence of CVD is an independent risk factor for kidney function decline with the risk worsening as the severity of renal dysfunction deteriorates (Kosmas et al., 2018; Subbiah, Chhabra, & Mahajan, 2016). Additionally, along with traditional risk factors, air pollution exposure is another important risk factor for impaired kidney function as a significant portion of cardiac output is delivered to the kidneys for filtration and is where these environmental toxins can be concentrated (Afsar et al., 2019; Wang et al., 2020; Xin, Sheng, Hanying, & Fan Fan, 2018).

Kidney function can be reflected by bio-indicators such as urinary concentrations of albumin, creatinine and the albumin-creatinine ratio (ACR). Albumin is the most

common protein found in urine and it would be normal to see small amounts excreted in the urine of healthy individuals. Albuminuria is increased excretion of urinary albumin and is considered to be an independent primary surrogate marker of kidney damage that can be related to diabetic nephropathy (Jenks et al., 2017). It is also a strong independent risk predictor of CVD (Kosmas et al., 2018; Özyilmaz, Bakker, de Zeeuw, de Jong, & Gansevoort, 2010; Thoenes et al., 2007).

ACR is commonly used clinically to detect elevated albumin excretion and is calculated by dividing the albumin concentration by creatinine concentration (Williams et al., 2018). The ACR is considered the 'gold-standard' test for the determination of microalbuminuria[∞], and elevations are indicative of possible kidney disease and disease related to hypertension (Table 2.6) (Williams et al., 2018).

Diagnostic values adopted by the RACGP are shown in Table 2.6.

Table 2. 6 Australian ACR diagnostic values.

	Females	**Males**
Normal, mg/mmol	< 3.5	< 2.5
Microalbuminuria, mg/mmol	3.5 - 35	2.5 - 25

Source: Royal Australian College of General Practitioners (2019).

2.6.6.1 Review of the literature

In recent times, observational studies have focused on understanding the relationship between renal function and air pollution exposure (H.-J. Kim, Min, Seo, & Min, 2018; Mehta et al., 2016; M. S. O'Neill et al., 2008) as a decline in renal function or chronic kidney disease (CKD) is known to be closely linked to CVD (Sarnak et al., 2003).

Several researchers have hypothesized that exposure to PM influences renal function via mechanisms similar to those proposed for CVD such as inflammation or oxidative stress (Afsar et al., 2019; Bowe et al., 2017; Bowe, Xie, Yan, Xian, & Al-Aly, 2020; Mehta et al., 2016; M. S. O'Neill et al., 2008). In addition to the various other well

[∞] Microalbuminuria describes a moderate increase in the level of urine albumin. It occurs when the kidney leaks small amounts of albumin into the urine. The condition is defined by an abnormally high permeability for albumin in the glomerulus and can be a sign of underlying conditions such as kidney disease or CVD (Williams et al., 2018).

established traditional CVD risk factors such as high BP and diabetes, an increasing body of evidence suggests that air pollution may be a novel environmental risk factor for declining renal function or CKD (S.-Y. Chen et al., 2018).

In a study by M. S. O'Neill et al. (2008), associations between ambient PM exposure with urinary albumin excretion was evaluated. Urinary albumin excretion is a sub-clinical marker of microvascular renal function, which predicts cardiovascular events. The study population for this research was recruited from the ongoing longitudinal MESA cohort which consists of 6814 participants aged between 44 – 84 years, who are free of CVD. Data related to ambient PM_{10} and $PM_{2.5}$ exposure was estimated from the regional monitoring network for 1 month, 2 months and 2 decades before the first visit. Urinary albumin and creatinine levels were determined from a spot sample taken in a fasting state. In adjusted models, chronic and recent PM exposures were not associated with albumin excretion (measured as ACR) per 10 $\mu g/m^3$ increase of PM_{10} or $PM_{2.5}$ (-0.02; 95% CI: -0.07, 0.03) with the authors concluding that ACR was not a strong mechanistic marker for the possible influence of air pollution on CV health in this sample. No associations were observed between $PM_{2.5}$ and ACR (M. S. O'Neill et al., 2008).

In more recent studies, associations between renal function and exposure to ambient air pollutants have been explored using estimated glomerular filtration rate (eGFR) as an alternative indicator for renal function (Bowe et al., 2017; H.-J. Kim et al., 2018; Lue, Wellenius, Wilker, Mostofsky, & Mittleman, 2013; Mehta et al., 2016). In all studies, exposure to pollutants was estimated using annual mean concentrations obtained from spatiotemporal models or data from ambient monitoring stations and attributed to adult study populations located in the US (Bowe et al., 2017; Lue et al., 2013; Mehta et al., 2016), Taipei (Y.-R. Yang et al., 2017) and Korea (H.-J. Kim et al., 2018).

Mehta et al. (2016), using longitudinal data from 669 older men in the Veterans Administration Normative Aging Study, and Lue et al. (2013), using cross-sectional data from 1103 patients hospitalized following a CV event, found an IQR increase in $PM_{2.5}$ exposure to be associated with reduced eGFRs (representing reduced renal function) (Mehta et al., 2016). Furthermore, living closer (within 50 m) to major highways (where NO_2 is often used as the surrogate air pollutant) was reported to significantly lower eGFRs when compared with those who lived further away (> 1000

m) (Lue et al., 2013). In one of the largest studies to date using data from the Department of Veteran Affairs (n = 2 010 398), Bowe and colleagues (2017) examined associations between PM_{10}, NO_2 and CO concentrations with multiple measures of kidney function, including eGFR. A deterioration in renal function (measured as an eGFR decline of $\geq 30\%$) was reported with an IQR increase in concentrations of PM_{10}, NO_2 and CO (Bowe et al., 2017).

Yang and colleagues (2016) evaluated the association between renal function and PM (PM_{10} and $PM_{2.5}$) among Taiwanese adults. Significant adverse associations were reported between renal function indicators including eGFR with PM (Y.-R. Yang et al., 2017).

Finally, using nationwide data from 24 407 Korean adults, H.-J. Kim et al. (2018) investigated exposure to ambient concentrations of PM_{10}, NO_2 and CO with renal function, measured as eGFR. The authors reported that a 10 $\mu g/m^3$ increase in PM_{10} and a 12 ppb increase in NO_2 was associated with decreases of 0.46 and 0.85, respectively, in eGFR (all $p < 0.05$) (H.-J. Kim et al., 2018).

In conclusion, whilst ambient air pollutants including PM and some gaseous pollutants have been associated with various risk factors related to CVD (D. G. Bell et al., 2017; R. D. Brook et al., 2016; Fiordelisi et al., 2017; Jaganathan et al., 2019; Rajagopalan et al., 2018; S. Rajkumar et al., 2018; C.-F. Wu et al., 2016; X. M. Wu et al., 2019), and although environmental air pollution exposure is considered a risk factor for kidney dysfunction, studies investigating this relationship are rare and findings have been inconsistent (Afsar et al., 2019; Bowe et al., 2017; Bowe et al., 2020; H.-J. Kim et al., 2018; Lue et al., 2013; Mehta et al., 2016; M. S. O'Neill et al., 2008; Wang et al., 2020). Additionally, scientific efforts have focused primarily on exposure to PM air pollution, with little evidence of the relationship between renal function and other pollutants (Bowe et al., 2017; B. Bowe et al., 2018; H.-J. Kim et al., 2018; Mehta et al., 2016; Wang et al., 2020).

2.7 Mechanistic evidence

Whilst the link between ambient air pollution exposure and adverse cardiometabolic outcomes is clearly established (R. D. Brook et al., 2010; Rajagopalan et al., 2018), the

mechanisms whereby this association exists remains to be fully elucidated (Bräuner et al., 2008; Jaganathan et al., 2019; F. J. Kelly & Fussell, 2012; S. A. Lucht et al., 2018).

A variety of different approaches have been adopted to study the effects of air pollution on pathophysiological pathways (M. R. Miller & Newby, 2020; T. Munzel et al., 2017a) and although there remains much to be understood, our appreciation of the physiological effects and plausible biological mechanisms that link air pollution exposure with mortality and morbidity is evolving rapidly and continues to do so (F. J. Kelly & Fussell, 2012, 2015; Rajagopalan et al., 2018).

Although air pollution can exert direct negative effects on the cardiometabolic systems including oxidative stress in the lungs leading to a chronic, systemic inflammatory response, inflammation of adipose tissue, plasma viscosity, insulin resistance and metabolic syndrome (Cicoira, 2018; B. A. Franklin et al., 2015; M. R. Miller & Newby, 2020; Rajagopalan et al., 2018; Rajagopalan & Brook, 2012; Qinghua Sun et al., 2010), it is important to understand that these pathophysiologic events can modulate traditional risk factors leading to autonomic imbalance, endothelial dysfunction, altered arterial diameter (Urch et al., 2004) or vascular tone and changes in heart rate, all of which ultimately can result in increased blood pressure and hypertension (M. R. Miller & Newby, 2020; Mills et al., 2008; Urch et al., 2004).

Similarly, these sub-clinical outcomes may contribute to diabetogenic metabolism and eventually lead to the inception of T2DM (B. A. Franklin et al., 2015; Rajagopalan & Brook, 2012). This is supported by limited, but recent evidence, that exposure to ambient air pollutants including PM (PM_{10}, $PM_{2.5}$) and some gaseous pollutants (NO_2) may increase the risk of T2DM in the general population (Balti et al., 2014; I. C. Eze et al., 2015; Sung Kyun Park, 2017; S. K. Park & Wang, 2014)

Difficulties also exist in that these pathways are not mutually exclusive, and may be activated at different time frames following exposure to pollutants, and vary in relation to exposure duration and dose (B. A. Franklin et al., 2015). Some pathways have more relevance to short-term exposures (e.g., autonomic imbalance [which may lead to changes in BP], systemic inflammatory response [which may play a role in the chronic development of atherosclerosis and insulin resistance/T2DM]) and likely factor mostly in a triggering role. Others will play a more long-term role, and underlying susceptibilities and comorbidities may also have a function in determining the

preeminent pathways elicited in an individual. Additionally, other environmental factors (e.g., co-pollutants, noise) may also modify patient-level responses (B. A. Franklin et al., 2015; T. Munzel et al., 2017a).

However, what remains to be understood as the fundamental question is what are the primary initiating pathways of secondary effects (B. A. Franklin et al., 2015; Rajagopalan et al., 2018).

2.8 Animal evidence

In addition to epidemiologic data, animal data has provided convincing evidence and suggested potential mechanisms of the role air pollution may play in cardiometabolic dysfunction (Sung Kyun Park, 2017; Qh Sun et al., 2005; Q. Sun et al., 2009; Xu et al., 2010).

J. Araujo et al. (2008) compared proatherogenic effects of ambient PM ($PM_{2.5}$, UFP) in mice and found larger early atherosclerotic lesions in mice exposed to UFP compared to $PM_{2.5}$ or filtered air (J. Araujo et al., 2008). Similarly, in an earlier study, L. C. Chen and Nadziejko (2005) demonstrated that sub-chronic exposure to ambient PM in mice had a significant impact on the size, severity and composition of aortic (atherosclerotic) plaques.

In murine models, $PM_{2.5}$ exposure has shown to contribute to the development of T2DM through the induction of adipose tissue inflammation and impaired blood glucose and insulin resistance (Haberzettl et al., 2016; Q. Sun et al., 2009), impaired glucose metabolism in the liver (Zheng et al., 2013) and an imbalance between white and brown adipose tissue (leading to metabolic dysfunction) (I. C. Eze et al., 2016; Xu et al., 2010).

Q. Sun et al. (2009) reported that long-term ambient $PM_{2.5}$ exposure led to impaired glucose tolerance, whole-body insulin resistance and systemic inflammation in a high-fat diet-induced obesity mouse model.

Interestingly, a further study revealed that young mice exposed to $PM_{2.5}$ beginning at 3 weeks of age developed homeostatic insulin resistance after 10 weeks of exposure without additional stress (such as diet-induced obesity) indicating a developmental

window of susceptibility to the effects of PM (Hamanaka & Mutlu, 2018; Xu et al., 2010).

Furthermore, exposure to PM has been implicated as a contributor to sub-optimal renal function. Experimental evidence in murine models indicates that inhalation of $PM_{2.5}$ leads to significant injurious structural and functional kidney abnormalities such as fibrosis, mesangial expansion and decreases in glomerular and tubular lumen volumes in the kidneys (Tavera Busso, Mateos, Juncos, Canals, & Carreras, 2018; Yan et al., 2014)

2.9 Indoor air and personal exposure studies

The indoor environment is filled with a vast and heterogenous mix of air pollutants originating from consumer products, heating and cooking appliances, cigarettes, electronic cigarettes, volatile organic compounds from organic solvents, furniture and of course respiring humans (Argacha et al., 2018; Bourdrel et al., 2017; Hoskins, 2011; Schripp, Markewitz, Uhde, & Salthammer, 2013).

The literature supports that in high-income countries, most daily time is spent indoors and because of this, indoor spaces, and particularly the domestic environment where up to two thirds of individual daily time is spent (Brasche & Bischof, 2005; Lai et al., 2004; Leech et al., 2002; Newby et al., 2015; Schweizer et al., 2007), it would seem an important micro-environment to monitor when considering the impact of air pollution on health.

However, studies linking indoor residential exposures with associated health effects, are limited (Magalhaes, Baumgartner, & Weichenthal, 2018).

Additionally, most studies conducted to date have been conducted in lower- and middle-income countries where air quality – in both indoors and outdoors – are different and significantly poorer than in high-income countries (J. Baumgartner et al., 2018; J. Baumgartner et al., 2011; Kephart et al., 2020; Krassi Rumchev et al., 2018). Many studies also report associations between adverse health outcomes with ambient levels of various air pollutants using data estimated from regional monitoring sites (Giorgini et al., 2016; Kephart et al., 2020), modelled concentrations (B.-Y. Yang, Qian, et al., 2018) or other area-based type measurements (Northcross et al., 2015).

Difficulties exist with using modelled and ambient concentrations as a surrogate measures for personal or indoor exposure assumes that individuals are equally exposed to pollutants within a region at a time (R. D. Brook et al., 2011) leading to degrees of potential exposure misclassification (Giorgini et al., 2016). Indeed fixed site outdoor monitors and estimated exposures have previously been reported in the literature as poor estimates of personal exposures to air pollutants with high spatial variability (Kephart et al., 2020; Northcross et al., 2015).

In a recent study in Perth, Western Australia, associations between residential indoor PM, measured for 24-hours, and clinic BP was investigated in 41 non-hypertensive adult participants, aged between 18 and 65 years. In a model adjusted for age and gender only, it was found that a one IQR increase in TPM (32.25 $\mu g/m^3$) was associated with a 6.97 mmHg (95% CI: 2.16, 11.79; $p < 0.01$) higher SBP, and a 3.69 mmHg (95% CI: 0.84, 6.54; $p < 0.05$) higher DBP. With full adjustment to the model, the effect on SBP was further increased (13.44 mmHg: 95% CI: 4.07, 22.81; $p < 0.01$), however was diminished to non-significance with DBP (4.64 mmHg: 95% CI: -1.48, 10.76) (Krassi Rumchev et al., 2018).

In a cardiovascular sub-study of the Detroit Exposure and Aerosol Research study (DEARS), daily changes in community ambient versus personal level $PM_{2.5}$ and its association with differential effects on BP was investigated in 65 non-smoking adults (aged 44.6 ± 15.7 years). Personal $PM_{2.5}$ data was collected using personal environmental monitors and ambient community data was collected from a fixed site monitor located in the local area. Mean daily personal and community measures of $PM_{2.5}$ were 21.9 ± 24.8 $\mu g/m^3$ and 15.4 ± 7.5 $\mu g/m^3$, respectively. Resting supine BP was measured using an automated non-ambulatory device. The findings of this study showed community $PM_{2.5}$ levels were not associated with either systolic or diastolic BP. However, in adjusted models, a 10 $\mu g/m^3$ increase in total personal level $PM_{2.5}$ exposure was associated with a 1.41 mmHg (95% CI: 0.763, 2.057; $p < 0.001$) higher SBP, one day after exposure. No relationship was observed between $PM_{2.5}$ exposure at community or personal level with DBP (R. D. Brook et al., 2011).

In a subsequent and similar DEARS sub-study of 51 non-smoking adults, the same authors observed no consistent relationships between PM levels (daily mean personal $PM_{2.5}$ level: 18.0 ± 10.4 $\mu g/m^3$; daily mean ambient $PM_{2.5}$: 15.8 ± 7.6 $\mu g/m^3$) with BP

when total personal $PM_{2.5}$ exposure was measured each hour, during routine daily activity throughout the preceding 24-hour period (Robert D. Brook, Hwashin H. Shin, et al., 2011).

Similarly, in a longitudinal study conducted in Windsor, Canada, 28 non-smoking seniors aged 65 + were recruited to investigate BP changes associated with exposure to short-term (24-hours) PM air pollution. Indoor and outdoor air quality monitoring was conducted at the residence and participants wore an active personal monitor to measure their continuous exposure to $PM_{2.5}$ over 24-hours. Pollutant levels were considered low with mean concentrations of personal, indoor and outdoor $PM_{2.5}$ of 6.3 $\mu g/m^3$; 6.8 $\mu g/m^3$ and 15.3 $\mu g/m^3$, respectively. Systolic and diastolic BP was measured during a clinical assessment using a non-ambulatory automated device. In this study, an IQR increase in personal $PM_{2.5}$ concentration (IQR: 7.1 $\mu g/m^3$) was significantly associated with a 3.43 mmHg ($p < 0.05$) higher SBP, but not with DBP. In contrast, an IQR increase in indoor monitored $PM_{2.5}$ (IQR: 3.5 $\mu g/m^3$) was significantly associated with a 3.38 mmHg ($p < 0.05$) higher DBP, and a non-significant 0.61 mmHg higher SBP (L. Liu et al., 2009).

In studies conducted in China where much higher levels of indoor and outdoor pollution are consistently shown (Lim & Thurston, 2019; Riant et al., 2018), no association was found in 240 rural Chinese children exposed to high personal levels of $PM_{2.5}$ (mean: 53.0 $\mu g/m^3$) from biomass combustion sources, with BP (Jill Baumgartner et al., 2012). This is in contrast to a similar study of 280 non-smoking women (mean age 51.9 years) in the same rural China location exposed under similar conditions to high levels of personal $PM_{2.5}$ (median: 52 $\mu g/m^3$ in summer and 105 $\mu g/m^3$ in winter), where a 1-log-$\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with a 2.2 mmHg (95% CI: 0.8, 3.7; $p = 0.003$) higher SBP, and a 0.5 mmHg (95% CI: -0.4, 1.3; $p = 0.3$) higher DBP (J. Baumgartner et al., 2011).

Indoor and personal environment exposures to gaseous pollutants, which have historically not been well studied, are beginning to attract more recent scientific attention.

Everson and colleagues (2019) undertook a longitudinal cohort study in the Cape Town region of South Africa investigating low level personal NO_2 exposure in females, with measures of BP. Sixty-one healthy mixed-race females wore personal NO_2 sampling

monitors for 7-days to produce an average concentration for the 7-day monitoring period. The results of this study showed NO_2 exposure was positively associated with BP in adjusted models, and each SD increase (4.96 μg/m^3) in NO_2 was associated with a 2.42 mmHg (95%CI: 0.03, 4.80 mmHg; p = 0.047) and 1.76 mmHg (95%CI: 0.00, 3.52 mmHg; p = 0.050) higher SBP and DBP, respectively. This was despite 7-day personal NO_2 exposure concentrations observed during the study (range: 2.94 μg/m^3 – 25.35 μg/m^3) remaining below the recommended WHO, European Union and South African air quality standards for NO_2 (annual exposure of < 40 μg/m^3; 1-hour exposure of < 200 μg/m^3) (Everson et al., 2019).

In the DEARS cardiovascular study, associations between personal exposure to individual species of VOC with BP and other CV health outcomes, was investigated in 65 non-smoking adults, aged 45.4 ± 15.4 years. Study participants wore a personal VOC monitor fixed to passively collect VOC samples for a 24-hour period. In the data analyses, these authors employed 'principal component' analysis to reduce the number of personal VOC and formed three source category groups including; VOC with a primary petroleum source (7 VOC species), a butadiene source (3 VOC species) or a freon and industry source (2 VOC species). Non-ambulatory BP measurements were obtained using standard procedures however, the average measurement was collected in the participants home whilst the VOC vest was being worn. Variable results were shown between personal exposures to these mixed origin VOC with cardiovascular physiology, although the authors concluded that VOC originating from these predominantly industrial and/or traffic related sources, may have rapid impacts upon the human cardiovascular system (Shin et al., 2015).

2.10 Limitations of the evidence

Whilst published literature has provided consistent and extensive evidence whereby exposure to air pollution may adversely affect a range of sub-clinical cardiometabolic risk markers, findings have generally been mixed whether the exposure has been short- or long-term, or involves low- or high-concentration exposures.

Between studies effect estimates consistently vary in magnitude (which might be as a result of heterogeneity of study designs), different exposure methodologies are used, individual study results are inconsistent, different clinical and sub-clinical endpoints

are used, and high degrees of study design heterogeneity requires for cautious interpretations of many of these effect sizes and limits the possibility of direct inter-study comparisons (Giorgini et al., 2016; Jaganathan et al., 2019; Rabito et al., 2020; B.-Y. Yang, Qian, et al., 2018).

CHAPTER THREE – METHODOLOGY

A detailed description of the study is provided in the following sections of this chapter incorporating the study design, location and population, recruitment and screening of participants and data collection. This chapter also provides details regarding the data analyses including the calculation of sample size, the creation of the data set/s and statistical analysis.

3.1 Study design and scope

A cross-sectional study conducted in a population of apparently healthy, middle-aged adults living in the metropolitan area of Perth, Western Australia (Figure 3.1).

The scope of this study is limited to exploring associations between single indoor residential air pollutants with various indicators of cardiometabolic risk. This study does not attempt to determine or consider air exchange rates (ventilation), characterise sources of emissions including secondary reaction pollutants, and does not contemplate multi-pollutant models.

3.2 Study location

Perth is the capital of Western Australia. It is a typical Australian capital city with a population of approximately 2.1 million people densely situated around the capital (Australian Bureau of Statistics, 2017).

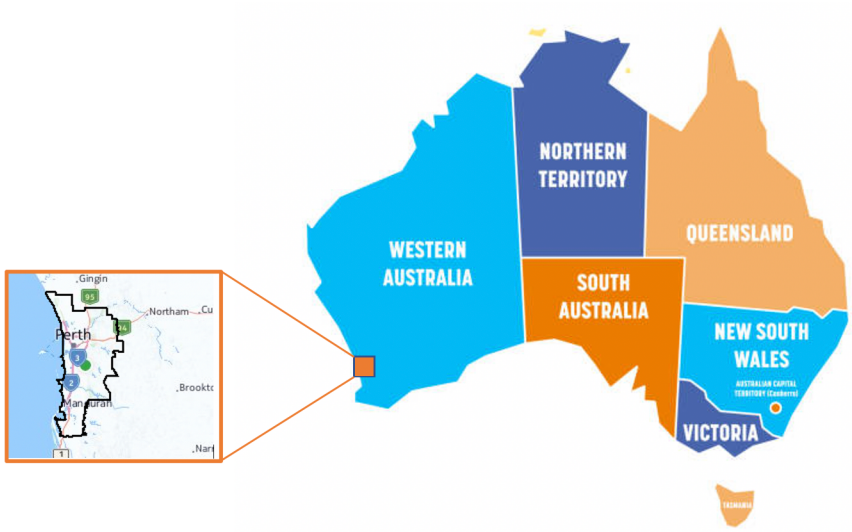

Figure 3. 1 *Map of the study location.*

In Perth, ambient air quality is considered to be of a high standard compared with other Australian and international cities (Government of Western Australia, 2018).

3.3 Study population

Participants were initially invited to join the study through local radio advertising (Curtin FM) and a generic group email to all staff at Curtin University. Further participants were recruited by word-of-mouth from already enrolled participants. Study participants were continuously recruited throughout the data collection period from March 2017 until May 2018.

Prior to enrolment, participants were either verbally screened for eligibility by a seven-question telephone interview or completed an electronic questionnaire (Qualtrics) addressing study inclusion and exclusion criteria.

Adults meeting the following criteria were eligible to participate in the study:

Inclusion criteria:

- Non-smoker living in a non-smoking household;
- Aged between 35 to 69 years;
- Willing to participate in all stages of the study.

Exclusion criteria:

- A history of cardiovascular events or medical diagnosis of CVD;
- Medically diagnosed diabetes;
- Use of anti-hypertensive or lipid modifying medications[1];
- Lack or withdrawal of written consent.

3.4 Ethical considerations

This study protocol was approved by the Human Research Ethics Committee at Curtin University (HRE2016-0308) (Appendix A).

Upon enrolment, study participants were provided with an information sheet which outlined the study procedure and voluntary nature of their involvement (Appendix B). Recruits were provided the opportunity to ask the investigator further questions following which full written, informed consent was obtained (Appendix C). Details of the research team were contained on the participant information sheet.

3.5 Data storage and management

Each participant was assigned a unique alpha-numeric identification number to secure personal data. All paper and electronic files are managed and stored according to the Australian Code for the Responsible Conduct of Research. Electronic files are backed up, maintained and stored on Curtin University's secure R-drive, and hard copy original material including questionnaires and time-activity data are stored in numerical order, in a locked compactus, in a secure entry room. Access to the study data is restricted, and participant files will be maintained in storage for a period of seven years after completion of the study according to National Health and Medical Research Council (NHMRC) requirements.

[1] Some examples include alpha blockers, angiotensin II receptor blockers, ACE inhibitors, beta-blockers, calcium channel blockers, diuretics, vasodilators, antihypertensive combinations, statins or insulin.

3.6 Data Collection

Data collection for each participant involved a two-stage process ("home stage" and "clinic stage") which is illustrated in Figures 3.2 and 3.3. All data collection and assessments were carried out by the same investigator following standard protocols. Participants were offered the opportunity to select the stage that was undertaken first, however both stages were to be completed within a 14-day maximum time period (determined by equipment availability, investigator availability and participant preference). Both stages are described in further detail below.

3.6.1 Home stage – 24-hour in-home assessment

During the home stage shown in Figure 3.2, indoor and outdoor pollutant concentrations and ambulatory BP were measured. Participants were also provided with two questionnaires ('health' and 'domestic environment') and a time-activity diary to complete.

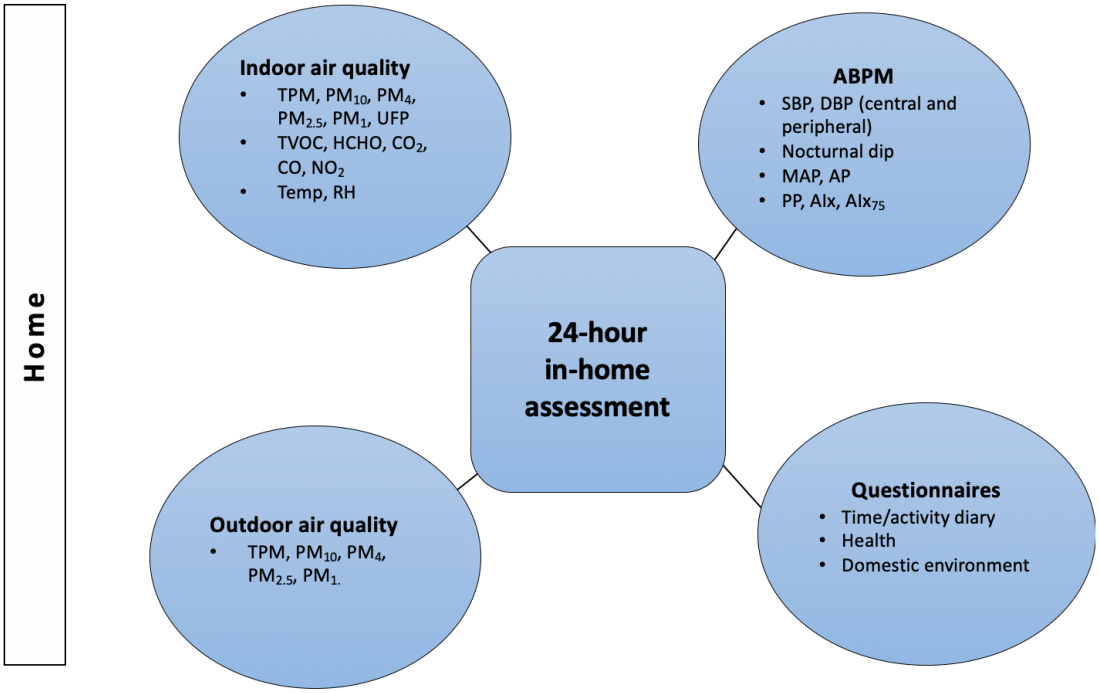

Figure 3. 2 *Components of the 24-hour in-home assessment.*

Residential indoor and outdoor pollutant concentrations and ambulatory BP and hemodynamic indices were measured over one concurrent 24-hour period and participants were requested to undertake their daily tasks and activities, and maintain their household as usual during the monitoring period. The same instructions regarding air monitoring, measurement of ambulatory blood pressure and the filling out of study questionnaires were provided to each participant.

At the completion of the 24-hour (± 2-hour) monitoring period, air quality equipment, ambulatory BP monitor and completed questionnaires were collected by the investigator from participants' home.

3.6.1.1 Measurement of indoor air pollution

Indoor air pollutant concentrations were measured in the main living area and instruments were co-located on the same trolley used throughout the entire study (Wheeler, Xu, et al., 2011).

Data was collected on;

- Particulate matter in five size fractions including total particulate matter (TPM), PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP;
- Gaseous pollutants including formaldehyde (HCHO), total volatile organic compounds (TVOC), nitrogen dioxide (NO_2), carbon monoxide (CO) and carbon dioxide (CO_2) and;
- Ancillary measurements including temperature and relative humidity (RH).

UFP measurements were undertaken for a 6-hour period between 4pm and 10pm due to operational limitations of the equipment and the in-home assessment was commenced at a time convenient to participants prior to 4pm.

3.6.1.2 Measurement of outdoor air pollution

Outdoor measurements were conducted for PM (TPM, PM_{10}, PM_4, $PM_{2.5}$ and PM_1) only due to limitations with equipment availability. Outdoor air monitoring equipment was placed in the closest powered location to the house, under shade for protection from

rain and sunlight (Bhangar et al., 2011), and away from any combustion sources such as barbeques and driveways (Wheeler, Xu, et al., 2011).

Indoor and outdoor residential sampling was conducted at 1.5m which is the approximate breathing zone of a standing adult (Wheeler, Xu, et al., 2011). Air sampling was undertaken on both weekdays and weekends as published research indicates that mass concentrations of PM do not differ in relation to days of the week (Yoda, Tamura, & Shima, 2017).

3.6.1.3 Air quality instrumentation

Indoor and outdoor particle mass concentrations (PM) was determined by using a DustTrak DRX ($\mu g/m^3$; DustTrak DRX 8533. TSI Inc., Shoreview, MN, USA). UFP number concentration was measured by using a P-Trak 8525 ($particles/cm^3$; P-Trak model 8525. TSI Inc., Shoreview, MN, USA).

The DustTrak DRX 8533 is a light-scattering laser photometer that simultaneously measures real-time aerosol mass readings for five PM size fractions (TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1) and displays particle mass concentrations in units of micrograms per cubic metre ($\mu g/m^3$; g x 10^{-6}). DustTrak uses a laser (780 nm) to illuminate particles that are drawn into a sensing chamber in a continuous stream by a diaphragm pump (TSI Inc., 2012a; L. A. Wallace et al., 2011). Part of the stream is split before entering the sensing chamber and passed through a HEPA filter before being injected back into the chamber as sheath flow (TSI Inc., 2012a). This sheath flow, called the sample flow, is illuminated by a laser sheet from a laser diode. The light emitted from the laser diode is focused with lenses and the intensity is determined by photodetector (TSI Inc., 2012a; L. A. Wallace et al., 2011). Size segregated mass concentrations are a function of the total particle volume, the index of refraction and the particle composition (L. A. Wallace et al., 2011). The measuring range of the instrument is 1 $\mu g/m^3$ to 150 x 10^3 $\mu g/m^3$ with accuracy of ± 0.1% of the reading or 1 $\mu g/m^3$, whichever is greater.

Two DustTrak 8533 instruments were used at each dwelling to simultaneously measure indoor and outdoor air quality (Wheeler, Wallace, et al., 2011; Wheeler, Xu, et al., 2011) over the full 24-hour monitoring period. Bi-monthly (± 2 weeks), instruments were run in a side-by-side configuration to assess accuracy. Additionally, both units were externally factory calibrated, twice each, over the data collection period.

DustTrak's were fitted with a 37mm polyvinyl chloride (PVC) filter with a pore size of 5 μm (SKC Inc, USA) and operated with the factory set flow rate of 3.0 L/min. Instruments were factory calibrated for flow rate prior to the commencement of the project, and flow rates were intermittently checked during the course of the project using a calibrated rotameter (TSI LPM-air).

Zero calibration for both instruments was conducted on-site prior to the commencement of data logging to minimise the effect of zero drift. Zero calibration was undertaken by attaching the zero filter and running the 'zero cal' function. Both DustTrak instruments were pre-set with residential location details before commencing monitoring and were programmed to log data at 5-minute intervals for the full 24-hours.

A portable P-Trak 8525 was used to detect and count UFP < 1 μm in real-time. P-Trak displays the measured particle concentration in units of particles per cubic centimeter (particles/cm^3) and the instrument's measuring range is 0 to 5 $x10^5$ particles/cm^3 (TSI Inc., 2012b). Concentrations are determined by passing particles through a saturator tube where they mix with isopropyl alcohol which condenses on the particles (TSI Inc., 2012b; L. A. Wallace et al., 2011). This results in particle growth to a size at which they can be detected and counted as they pass through a focused laser beam which produces flashes of light sensed by a photodetector (TSI Inc., 2012b; L. A. Wallace et al., 2011). Particle concentration is determined by counting the light flashes (TSI Inc., 2012b). Flow rate for the sampling is approximately 100 cm^3/min (Akbar-khanzadeh et al., 2012). The isopropyl alcohol saturated wick used by P-Trak has a limit of operation of 8-hours at 21°C before requiring re-saturation (TSI, n.d.). For this reason, the instrument was programmed to measure for a continuous 6-hour period only, between 4pm to 10 pm, with data being logged at 5-minute intervals.

Data from both the DustTrak 8533 and P-Trak 8525 was downloaded using TrakPro data analysis software.

Gaseous pollutants were measured using the Gray Wolf AdvancedSense Pro fitted with a sensor probe measuring total volatile organic compounds (TVOC; ppb), carbon dioxide (CO_2; ppm), carbon monoxide (CO; ppm), nitrogen dioxide (NO_2; ppm), temperature (°C) and relative humidity (%RH) (Advanced Sense Pro. Gray Wolf Sensing Solutions, Shelton, CT, USA). A separate, supplementary monitor was attached to the AdvancedSense Pro measuring formaldehyde (HCHO; $\mu g/m^3$)

(Formaldehyde Multimode Monitor FM-801. Gray Wolf Sensing Solutions, Shelton, CT, USA).

The AdvancedSense Pro measures TVOC using photoionization detectors (PID) within the range of 5 ppb to 20 000 ppb, with a resolution of 1 ppb and limit of detection of < 5 ppb. This PID is calibrated to isobutylene and measures VOC to 10.6 eV. It does not respond to VOC with ionisation potentials > 10.6 eV such as ethane, methane or HCHO. CO_2 is measured using a non-dispersive infrared (NDIR) gas sensor which measures within the range of 0 ppm to 10 000 ppm. The accuracy of this sensor is ± 3% reading to ± 50 ppm. CO is measured using an electrochemical type gas sensor that measures within the range of 0 ppm to 500 ppm. The accuracy of this sensor is ± 2 ppm < 50 ppm, ± 3% reading at > 50 ppm. All sensors exhibit 90% response in < 1 minute. The AdvancedSense Pro was factory calibrated six-monthly, and intermittently run in a side-by-side configuration with a factory provided matching unit, to test for accuracy and reliability.

The multimode monitor measures concentrations of HCHO using the photoelectric absorptiometric principle and detects in the range of < 25 $\mu g/m^3$ to 1230 $\mu g/m^3$ (< 20 ppb to 1000 ppb) with limits of detection down to < 5 ppb. The accuracy of this sensor is ± 4 ppb < 40 ppb, ± 10% of reading ≥ 50 ppm. A reusable sensor cartridge measures HCHO by utilizing the chemical reaction between HCHO and β-diketone in a porous glass. The reaction was measured via photoelectric photometry.

Both instruments were pre-set with residential location details before commencing monitoring and programmed to log data at 30-minute intervals.

Data from the AdvancedSense Pro and HCHO multimode monitor was downloaded using WolfSense data analysis software.

3.6.1.4 Measurement of ambulatory blood pressure and instrumentation

An ambulatory BP monitor (ABPM) (Oscar 2, Sun Tech Medical Inc., USA) was fitted to the left arm of the participant, having been pre-programmed to obtain readings at 30-minute intervals for the full 24-hours (O'Brien et al., 2013; O'Flynn et al., 2015; Parati et al., 2014). All participants were provided with the same instructions and were advised to remain still with the forearm extended during each BP reading (O'Flynn et al., 2015).

Each BP measurement took approximately 30 seconds to perform. The device was programmed to automatically attempt a subsequent measurement 4-minutes later if the previous was unsuccessful due to participant movement or positioning.

Data collected from ABPM included:

- 24-hour central and peripheral systolic BP (SBP); 24-hour central and peripheral diastolic BP (DBP); day-time central and peripheral SBP and DBP; night-time central and peripheral SBP and DBP (all BP measurements in mmHg); 24-hour, day-time and night-time heart rate (beats per minute; bpm); central and peripheral systolic and diastolic nocturnal dip (%);
- Component hemodynamic and arterial stiffness measures including central augmentation index (AIx; %) along with AIx adjusted for heart rate (AIx_{75}; %); central and peripheral augmented pressure (AP); pulse pressure (PP) and mean arterial pressure (MAP) (all measured in mmHg).

Data was downloaded from the ABPM using AccuWin Pro (v4 Sun Tech Medical, Inc. USA) software.
Mean 24-hour BP was calculated as the mean of all the readings throughout the 24-hour period (Andreadis et al., 2016; O'Flynn et al., 2015). Awake and asleep periods were determined from time-activity diaries maintained by participants for the 24-hour monitoring period using the same method described in several other studies (O'Brien et al., 2013; Parati et al., 2014; Z. C. Sun et al., 2013). Editing of the 24-hour set of measurements was carried out to reflect self-reported awake and asleep times (Parati et al., 2014).

Following standard protocol described in Parati et al. (2014) and O'Brien et al. (2003), measurements were deemed as valid and included in the final analyses if 70% of the 24-hour measurements were obtained, and 20 valid awake and 7 valid asleep measurements were achieved. Where < 70% of 24-hour readings were achieved, further investigation was undertaken of edited daytime and nighttime readings. Daytime or nighttime measurements that did not pass validity criteria for the time period (daytime: 20 valid readings; night-time: 7 valid readings) were discarded and excluded from the final analyses by a process described in similar studies (Andreadis et al., 2016; O'Brien

et al., 2013). All valid daytime and nighttime readings were averaged to provide a single daytime and nighttime ABP value per study participant (Andreadis et al., 2016).

3.6.1.5 Questionnaires and time-activity diary

Each participant was provided with two questionnaires and a time-activity diary to be completed during the 24-hour monitoring period (Appendices D, E and F).

Participant demographics along with information on health and lifestyle behaviour was gathered by adapted version of the American Thoracic Society standardized IAQ and health questionnaire (Ferris, 1978) which has also been used in several other Australian studies (K. Rumchev et al., 2004; K. B. Rumchev et al., 2002; G. Zhang, Spickett, Rumchev, Lee, & Stick, 2004).

In the health questionnaire participants self-reported general demographic data including gender, age and address and other health related information including smoking status (yes, no), alcohol intake (more or less than two alcoholic drinks per day), medications taken, and comorbidities including conditions such as asthma, chronic obstructive pulmonary disease, kidney disease and thyroid conditions.

Using the collected demographic information, socioeconomic status (SES) was assigned using census-track data collected by the Australian Bureau of Statistics (Australian Bureau of Statistics, 2016). Post codes were used to rank participants homes according to relative socio-economic advantage and disadvantage using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (Australian Bureau of Statistics, 2016). The indexes are based on information from five-yearly Census of Population and Housing and uses information related to education, occupation and economic resources to create a distribution of scores. The distribution of scores is then divided into deciles, with a higher ranking signifying higher socioeconomic advantage (Australian Bureau of Statistics, 2016).

In this study, homes were situated in areas that ranked between two (low SES) and ten (high SES). For the purposes of statistical analysis, homes were divided into three equal groups according to rankings of low socioeconomic advantage (ranking 2-4), medium socioeconomic advantage (ranking 5-7) and high socioeconomic advantage (ranking 8-

10). Similar methods have been used in other studies (Chan et al., 2015; Roux et al., 2001).

Information related to the indoor environment was collected by questionnaire used in several previous studies examining IAQ (K. Rumchev et al., 2004; K. B. Rumchev et al., 2002; G. Zhang et al., 2004). Each participant reported on characteristics of their dwelling such as the age of the residence (< 10 years or > 10 years) and the number of household occupants. Sources of indoor air pollution was identified by survey questions related to type of cooking technology used (gas, electric or both), type of heating (flued and unflued gas, wood, coal, oil, kerosene, electric, reverse cycle air conditioning [A/C]) and cooling systems used (A/C, fans or combinations of both fans and A/C), floor and wall coverings, cleaning habits (frequency and types of products), distance of the residence to major roads (< 300m or > 300m) and garage location (attached to the home by inner door or not attached).

Participants also recorded their time-activity for the 24-hour monitoring period indicating for each two-hour period, their presence indoors/outdoors and where they were located (home/work/other). Other recorded activities included their sleep schedule (awake time; asleep time) or any situations which might be considered important to the study (e.g., stressful situations, unusual sleep times). Data collected using this method has been described in other similar studies (Buonanno, Stabile, & Morawska, 2014; Fuller et al., 2013; Steinle et al., 2015; Wheeler, Xu, et al., 2011).

3.6.2 Clinic stage – Fasting clinical assessment

Participants attended the Curtin University Clinical Health Suites for a health assessment (Appendix G) having fasted for 12 hours (other than water and regular medications) (G. L. Anderson et al., 2003).

Measurements and information collected during the assessment are illustrated in Figure 3.3 and included;

- A current health profile along with baseline health characteristics such as height, weight, hip and waist measurements;
- Resting seated BP;

- Blood and urine samples to establish a lipid and glucose homeostasis profile and renal function;
- Carotid-femoral pulse wave velocity (cfPWV) ascertained from a pulse wave analysis.

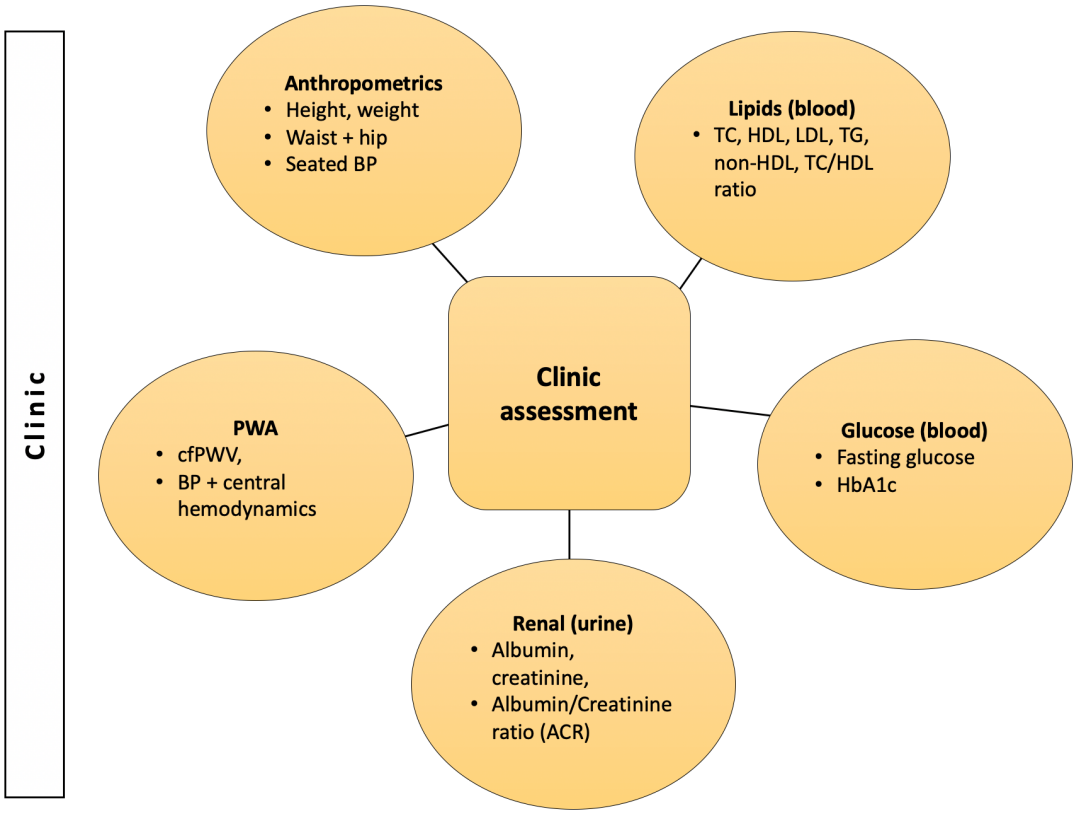

Figure 3. 3 *Components of the clinical assessment*

3.6.2.1 Anthropometrics

Participants' height (m) and weight (kg) were measured in bare feet and wearing light clothing. Weight was measured by mechanical scale (SECA 762, SECA, Germany) and height using a stadiometer (S+M. Surgical and Medical Products, Australia). Body mass index (BMI) was calculated by dividing body weight (kg) by the squared height (m^2) and is expressed in units of kg/m^2 (Sanchez-Inigo, Navarro-Gonzalez, Pastrana-Delgado, Fernandez-Montero, & Martinez, 2016; S. Wu et al., 2015).

Waist and hip circumference (cm) were measured using a non-stretch, retractable tape. Waist circumference was measured mid-way between the lowest rib and the iliac crest at the end of the participant's normal expiration. It is well reported in the literature that a larger waist, relative to hip measurement, indicates an increased risk for CVD (Huxley, Mendis, Zheleznyakov, Reddy, & Chan, 2010). As such, this study used waist circumference thresholds of < 94 cm for males and < 80 cm for females as recommended by the Australian Heart Foundation (AHF) to define low CV risk for this parameter (National Heart Foundation of Australia, 2016). After following standard protocol for identifying the level of the natural waist and hips and assuring the tape was level, the hip circumference was recorded. Waist-to-hip ratio was calculated by dividing the waist measurement by the hip measurement (G. L. Anderson et al., 2003; Dobbelsteyn, Joffres, Maclean, & Flowerdew, 2001).

3.6.2.2 Blood pressure

Brachial (peripheral) blood pressure (mmHg) was measured after 5 minutes rest in the sitting position in a quiet room. BP recordings on both arms were made using a digital automated monitor (Omron HEM-907; Omron Healthcare Co., Ltd. Kyoto, Japan). Three blood pressure measurements were taken with a one-minute interval between recordings. Further measurements were performed if the difference between SBP and DBP values of the second and third measurements was larger than 5 mmHg (deemed unstable), and the average BP levels were calculated on the basis of all readings from the second to the last measurements (Ji et al., 2017; O'Flynn et al., 2015; S. Wu et al., 2015) and was calculated independently for both arms.

3.6.2.3 Lipid, glucose and renal biomarkers

Two finger stick blood samples were collected using an aseptic technique. These samples were immediately analysed for lipids (total cholesterol [TC], high density lipoprotein [HDL], low density lipoprotein [LDL], non-HDL, triglycerides [TG], fasting glucose [all in mmol/L], and glycosated haemoglobin (HbA1c; %). A spot mid-stream urine sample was collected for determination of albumin (mg/L), creatinine (mmol/L) and albumin/creatinine ratio (ACR, mg/mmol). Lipids, HbA1c and urine analysis was conducted using appropriate reagent containing cassettes of the fully

automated biochemistry analysis system (Alere Afinion AS100, Waltham, MASS, USA).

Fasting glucose was analysed by a hand-held Accu-Chek Blood Glucose Meter (Roche Diabetes Care, Mannheim, Germany) using blood drawn from a finger stick test. The glucose meter reported blood glucose measurements in mmol/L.

3.6.2.4 Pulse wave analysis and pulse wave velocity

Central arterial pressures were derived from arterial pulse waveforms obtained from the right femoral artery and concurrent direct applanation tonometry of the right common carotid artery. Central pressures were measured non-invasively with the participant in the supine position, and calculated using the SphygmoCor device (EM3 XCEL, AtCor Medical Pty, West Ryde, Australia). Pressure waveforms were recorded from the brachial artery and corresponding central aortic pressure was derived using a generalized transfer function (C. M. McEniery, Cockcroft, Roman, Franklin, & Wilkinson, 2014). All recordings were performed on the right side of the body and transit distances were assessed by body surface measurements from the suprasternal notch to each pulse recording site (common carotid and femoral) (Figure 2.7) (Mitchell et al., 2010). Carotid-femoral PWV was determined by examining central arterial waveforms (Figure 2.6) obtained from the common carotid and femoral artery, and the time delay measured between the feet of the two waveforms. The distance covered by the waves was established as 80% of the distance between the two recording sites. All data was collected directly onto a laptop computer and processed with approved waveform analysis using a previously validated method (Butlin & Qasem, 2017). PWV was calculated by SphygmoCor proprietary software as distance/time delay in m/s (Butlin & Qasem, 2017; de Vos et al., 2017).

3.7 Data analysis

3.7.1 Creation of dataset

At the completion of data collection, raw data from each instrument was assessed against standard protocols for study validity. Data was only included in the final analyses if the individual study for each instrument was deemed valid against existing published standards or guidelines.

Due to instrument malfunction, a reduced dataset of only 40 households was achieved for UFP and a separate dataset was created which contained only those participants and households with a complete set of variables. All statistical analyses were run identically to the larger dataset of all other pollutants.

Descriptions of statistical analysis below are applicable to both the full dataset, and the reduced UFP dataset.

3.7.2 Sample size and effect

Assuming a conventional Cohen's medium effect size of 15%, a sample size of 110 was calculated by G power to achieve 80% power for testing both the overall significance of the univariate linear regression model, and an individual effect attributed to the domestic IAQ on selected cardiometabolic risk markers, at significance level of 5%. This medium effect size is equivalent to testing an overall multiple correlation of 0.13 and a partial correlation of 0.12, which are comparable with preliminary results from a recent Australian pilot study (n = 46) (Krassi Rumchev et al., 2018). The final sample size obtained was further verified by Green's formula for general practical applications using univariate regression analysis (Green, 1991).

3.7.3 Variables of interest

In this study, the primary outcome variable (dependent variable) was BP and included 24-hour, daytime and nighttime ambulatory SBP and DBP along with nocturnal systolic and diastolic BP dip.

Secondary outcome variables of interest included;

- 24-hour, daytime and nighttime central hemodynamic indices including AIx, AIx_{75}, AP, PP, MAP and PWV;
- Lipids including TC, HDL, LDL, TG, non-HDL cholesterol and TC/HDL ratio;
- Measures of glucose homeostasis including fasting glucose and HbA1c and;
- Renal function measures including albumin, creatinine and the ACR.

The primary exposure variables (explanatory/independent variable) of interest were indoor measurements of PM including TPM, $PM_{10,}$ PM_4, $PM_{2.5,}$ PM_1 and UFP along with gaseous pollutants TVOC, CO_2, CO, NO_2 and HCHO. Outdoor concentrations of TPM, $PM_{10,}$ PM_4,

$PM_{2.5,}$ PM_1 were also collected for comparison analysis with matched respective indoor concentrations.

Data on other covariates of interest was collected by questionnaire and is described at 3.6.1.5.

3.7.4 Statistical analysis

Descriptive statistics were produced to describe the profile and characteristics of study participants including demographic characteristics, health characteristics and participant's clinical cardiometabolic markers and to summarise air pollutant characteristics and home environment characteristics. Data values were expressed as mean (± standard deviation) for continuous variables and number (percentage) for categorical variables. Normality of all continuous data was assessed using histograms, boxplots, normal Q-Q plot and skewness and kurtosis coefficients.

Paired samples t-tests were undertaken to evaluate differences between daytime readings extracted from the 24-hour ABPM (peripheral daytime BP) and seated BP and clinic supine blood pressure (brachial BP), respectively. It is well established in the literature that central/aortic pressures are considered a more accurate and relevant representation of BP than peripheral pressures (C. M. McEniery et al., 2014; Palatini et al., 2014; T. G. Pickering, Shimbo, & Haas, 2006; Roman et al., 2007; Vlachopoulos et al., 2010) and as such, these were the data used in the final analysis.

Independent samples t-tests and one-way analysis of variance (ANOVA) were undertaken to determine the impact of selected house characteristics on concentrations of indoor air pollutants. Bonferroni post hoc comparisons were further conducted if overall significant differences were found based on the one-way ANOVA.

Bivariate association between every primary and secondary outcome variable, and each 24-hour average indoor pollutant concentration was examined by using the Pearson's correlation coefficient *r*, individually.

Multiple regression analysis using the general linear model (GLM) univariate procedure was then applied to investigate the association between each outcome variable including BP and all sub-clinical cardiometabolic biomarkers with individual indoor air pollutants with adjustment for confounders or covariates, separately.

Initial models were adjusted for potential covariates selected on the basis of similar studies that have previously been reported in the literature (Adar et al., 2018; R. D. Brook, Bard, et al., 2008; Chan et al., 2015; Z. Chen et al., 2016; Huxley et al., 2010; S. Rajkumar et al., 2018; Scheers et al., 2018; C.-F. Wu et al., 2016; X. M. Wu et al., 2019; Young et al., 2019). The present study design had effectively eliminated some potential confounders such as smoking, the presence of medically diagnosed hypertension (and subsequent use of anti-hypertensive medications), diagnosed dyslipidemia, historical CV events and/or a medically diagnosed pre-diabetic or diabetic profile (Lenters et al., 2010; Mehta et al., 2014) that may be involved in the causal mechanisms of vascular damage. Therefore age (continuous), gender (nominal; male, female), BMI (continuous), waist-hip ratio (continuous) and SES (ordinal; low, medium, high) were simultaneously adjusted in each individual multiple regression model.

To evaluate the influence of potential residual confounding effects on the final regression results, further covariates including temperature, relative humidity, waist circumference, ethnicity and alcohol consumption were added to additional regression models (Auchincloss et al., 2008; Scheers et al., 2018). No change in the effect direction was noted and effect estimates were not altered significantly with their inclusion, therefore they were excluded from the final model.

One participant was considered to have a contentious health and lifestyle profile (borderline hypertension; > 2 alcoholic drinks per day), however other cardiometabolic biomarkers were in the expected range. Sensitivity analysis was undertaken with this participant excluded, however no significant impact to the final results was observed following their exclusion.

Due to very large UFP concentration values compared to outcome values, UFP number concentrations were adjusted using the decimal scaling normalisation method described in other published literature (Eesa A.S. & Arabo W.K., 2017; Folorunso, Aibinu, Kolo, Sadiku, & Orire, 2018; Manimekalai & Kavitha, 2018). Using this method, and prior to regression analyses, UFP concentrations were divided by 10^3 to create a comparable measurement scale and enable meaningful, interpretable results. Similarly, CO_2 concentrations were also scaled by 10 to evaluate the association between this pollutant and blood and urine markers.

As the primary aim of this study was to investigate the relationship between domestic exposure to pollutants with pre-clinical cardiometabolic outcomes, adjustments were not made for covariates that represented sources of air pollution (e.g., cooking technology used, heating fuel, proximity to traffic sources). Multi-pollutant and co-pollutant models were also not explored in this study.

The final results were reported by mean change in the outcome variable corresponding to a one interquartile range (IQR) increase of exposure to each indoor pollutant concentration, along with its 95% confidence interval. A p-value ≤ 0.05 was considered statistically significant.

Data analyses were performed using IBM SPSS software (Version 24.0. IBM Corp, Armonk, New York, USA.).

CHAPTER FOUR – RESULTS

This chapter presents the findings of the study. The initial sections of the chapter provide descriptive statistics related to participant health and domestic environment. This is followed by a comprehensive statistical analysis identifying relationships between each individual indoor air pollutant with each sub-clinical outcome related to cardiometabolic risk.

4.1 Overview

For this study, 181 adults were recruited of which 70 were subsequently excluded due ineligibility with study criteria. Of the 70 excluded participants, 7 were not within the permitted age range, 11 were taking anti-hypertensive or lipid modifying medications, 9 expressed interest in participating in the study however did not respond to follow-up telephone calls or emails, and the remaining 43 withdrew prior to or without completing all phases of monitoring/assessments (Figure 4.1).

This corresponded to a study population of 111 subjects who provided outcome information related to selected cardiometabolic risk factors, along with matching information on exposures to indoor and selected outdoor pollutants. Additional information was also collected on covariates that were identified as important through examination of similar published studies (He, Morawska, & Mengersen, 2011; Morawska et al., 2001; Morawska, He, Hitchins, Mengersen, & Gilbert, 2003; Krassi Rumchev et al., 2018; K. Rumchev et al., 2004; K. B. Rumchev et al., 2002; Seguel, Merrill, Seguel, & Campagna, 2016).

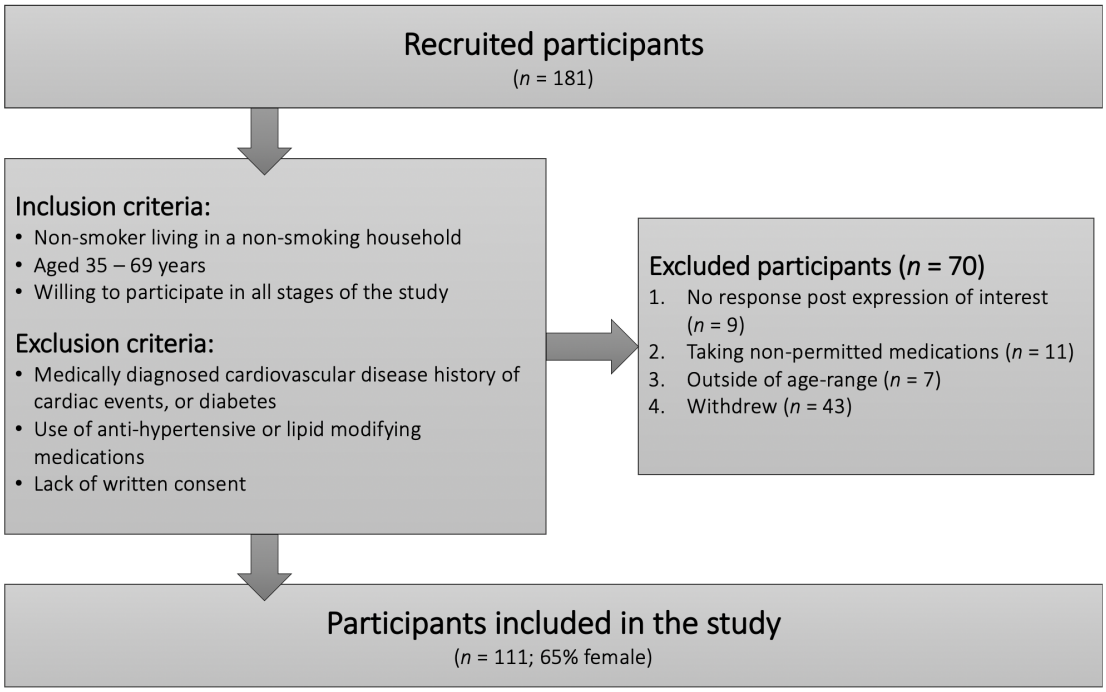

Figure 4. 1 *Recruitment of the study population.*

4.2 Study population characteristics

The mean age of the study population was 52.3 (standard deviation [SD] = 9.9) years, and 64.9% (n = 72) were female. Within the group, the average BMI was 24.9 (SD = 3.3) kg/m^2, with 51.4% (n = 57) of the study population falling into the normal weight category (between 18.5 – 24.9 kg/m^2) as defined by the World Health Organisation (WHO) (World Health Organisation, 2019).

The average waist measurement of the study population was 84.6 (SD = 11.7) cm. Both male and female average waist circumferences fell below the Australian Heart Foundation (AHF) recommended gender guidelines of < 94 cm for males, and < 80 cm for females. Within the study population, 64.1% of male participants recorded a waist measurement of < 94 cm, and 61.1% of females recorded a measurement of < 80 cm.

Whilst exclusion criteria of this study eliminated participants with cardiometabolic related conditions such as CVD or diabetes, some participants (n = 28; 25.2%) reported to suffering from a chronic condition which included exercise or cold-induced asthma, irritable bowel syndrome, or Crohn's disease. No participants were taking anti-hypertensive or lipid modifying medications, although 55.8% (n = 62) of participants

reported to taking vitamins, prescription medication (related to the above conditions) or a combination of both. Self-reported use of alcohol and medications along with the prevalence of comorbidities noted above, were low, and bivariate analyses indicated no meaningful associations between these, with any indoor pollutants.

No participants were smokers or lived with a smoker.

The majority of participants (n = 88; 79.3%) lived in higher socio-economic areas as defined by the Australian Bureau of Statistics Socio-Economic Indexes for Areas and described in Chapter 3.

Characteristics of the study population are summarised at Table 4.1.

Table 4. 1 Characteristics of the study population.

Characteristic	Mean ± SD	*n* (%)	Median (IQR)	min - max
Gender				
Male		39 (35.1)		
Female		72 (64.9)		
Age, y	52.3 ± 9.9		51.0 (16.0)	35 - 69
Height, cm	168.8 ± 10.4		167.4 (13.0)	151.4 - 202
Weight, kg	71.3 ± 13.5		70.0 (22.5)	44 - 111
BMI, kg/m^2	24.9 ± 3.3		24.8 (4.0)	18.8 - 33.1
Male	25.8 ± 2.8		26.1 (4.5)	20.2 - 30.6
Female	24.4 ± 3.5		23.8 (5.1)	18.8 - 33.1
Waist measurement, cm	84.6 ± 11.7		83.5 (15.5)	58 - 115
Male	92.8 ± 8.7		92 (12.0)	73 - 115
Female	80.0 ± 10.6		78 (14.0)	58 - 112
Hip-waist ratio	0.85 ± 0.08		0.85 (0.13)	0.69 - 1.05
Do you suffer from any chronic conditions?				
None		83 (74.8)		
Asthma, thyroid etc		28 (25.2)		
Medications				
None		49 (44.1)		
Vitamin supplements		27 (24.3)		
Prescription medication		23 (20.7)		
Combination vitamins and prescription meds		12 (10.8)		
SES, decile				
Low, 2-4		8 (7.2)		
Medium, 5-7		15 (13.5)		
High, 8-10		88 (79.3)		

n = 111; SD – standard deviation; IQR – interquartile range; min – minimum; max – maximum; y – years; cm – centimetres; kg – kilograms; BMI - body mass index; SES - socio-economic status

4.3 Household characteristics

Within each household, one occupant completed a questionnaire to provide information about the domestic environment and general household characteristics.

All study homes were non-smoking residences with the majority of houses aged ten years or older (*n* = 83; 75%). Most dwellings housed three or more occupants (*n* = 66; 59%) and approximately equal numbers of homes had ≤ 3 (*n* = 55; 50%), or 4+ bedrooms (*n* = 54; 49%).

More households cooked exclusively with gas (*n* = 25; 22%) than electricity (*n* = 20; 18%), although the majority of homes used combinations of both gas and electricity for cooking (*n* = 63; 57%). Most households reported to always or frequently using an extractor fan when cooking (*n* = 97; 87%).

Reverse cycle air conditioning was the preferred method of heating homes in winter (*n* = 46; 41%) and in summer, most people preferred to use combinations of air-conditioning and fans (*n* = 50; 45%).

Equal numbers of households reported to living in close proximity to a major highway as to not (*n* = 53; 48%).

4.4 Air quality

Indoor air pollutants including PM in five size fractions (TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1), gaseous pollutants (TVOC, CO_2, CO, NO_2 and HCHO) along with ancillary variables including temperature and relative humidity, were measured over a continuous 24-hour period. Due to equipment limitations, UFP was measured for a 6-hour period only in forty homes.

Outdoor concentrations of PM (TPM, PM_{10}, PM_4, $PM_{2.5}$ and PM_1) were simultaneously measured for the same 24-hour period as indoor PM.

The mean 24-hour indoor PM_{10} and $PM_{2.5}$ concentrations were 18.9 (SD = 22.2) $\mu g/m^3$ and 17.0 (SD = 21.8) $\mu g/m^3$ respectively, with ranges of 3.0 to 159.0 $\mu g/m^3$ for PM_{10} and 3.0 to 157.0 $\mu g/m^3$ for $PM_{2.5}$. Australian standards do not exist for indoor air pollutants, however of the study group, 96% of households were exposed to mean

indoor 24-hour PM_{10} concentrations that were less than or equal to the NEPM - AAQ standard of 50 μg/m^3. Similarly, 90% of households recorded 24-hour indoor concentrations less than or equal to the NEPM - AAQ $PM_{2.5}$ standard of 25 μg/m^3.

Across all size fractions, 24-hour mean outdoor concentrations of PM_{10} (25.0; SD = 35.1 μg/m^3) and $PM_{2.5}$ (22.1; SD = 35.0 μg/m^3) were also below the equivalent NEPM - AAQ and WHO air quality guidelines.

Concentrations between each respective PM indoor and outdoor size fraction (e.g., indoor PM_{10} vs outdoor PM_{10}) and all PM size fractions (e.g., indoor TPM vs outdoor PM_{10}, PM_4, $PM_{2.5}$ or PM_1), were not correlated suggesting that in this sample of homes, outdoor PM concentrations did not greatly influence indoor PM concentrations. No significant differences were found between the mean concentrations of indoor and outdoor measurements (TPM: $p = 0.122$; PM_{10}: $p = 0.074$; PM_4: $p = 0.101$; $PM_{2.5}$: $p = 0.116$; PM_1: $p = 0.129$).

Characteristics of indoor and outdoor pollutants along with ancillary measurements are summarized at Table 4.2.

Table 4. 2 Concentrations of air pollutants and ancillary measurements of study residences.

	Indoors			Outdoors		
Variable	**Mean ± SD**	**Median (IQR)**	**min-max**	**Mean ± SD**	**Median (IQR)**	**min-max**
Temperature, °C	23.6 ± 3.0	23.6 (4.9)	17.0 - 29.6			
RH, %	49.2 ± 8.2	48.6 (11.3)	26.6 - 72.2			
TPM, μg/m^3	21.1 ± 22.6	14.0 (15.0)	3.0 - 165.0	27.1 ± 35.3	17.5 (14.0)	6.0 - 277.0
PM_{10}, μg/m^3	18.9 ± 22.2	13.0 (13.0)	3.0 - 159.0	25.0 ± 35.1	16 (13.2)	6.0 - 276.0
PM_4, μg/m^3	17.4 ± 21.9	11.0 (11.0)	3.0 - 157.0	22.8 ± 35.0	14 (11.4)	4.0 - 275.0
$PM_{2.5}$, μg/m^3	17.0 ± 21.8	10.0 (10.5)	3.0 - 157.0	22.1 ± 35.0	13 (11.2)	3.0 - 274.0
PM_1, μg/m^3	16.5 ± 21.7	10.0 (10.5)	3.0 - 156.0	21.3 ± 35.0	12 (12.0)	3.0 - 273.0
UFP$^{\omega}$, particles/cm^3	11256.0 ± 8744.3	9218 (12756.8)	975 - 35941			
TVOC, ppb	406.6 ± 272.0	325.6 (124.7)	97.6 - 1888.4			
CO_2, ppm	470.0 ± 180.4	435.2 (291.8)	204.5 - 1059.5			
CO, ppm	0.94 ± 0.10	0.91 (0.15)	0.74 - 1.74			
NO_2, ppm	0.15 ± 0.03	0.15 (0.03)	0.09 - 0.29			
HCHO, μg/m^3	15.8 ± 4.9	15.0 (6.2)	10.0 - 36.0			

n = 111; SD - standard deviation; IQR - interquartile range; min - minimum; max – maximum; °C – degrees celcius; RH – relative humidity; % - percentage; TPM – total particulate matter; μg/m^3 micrograms per cubic metre; PM_{10} – particulate matter with an aerodynamic diameter < 10 μg/m^3; PM_4 – particulate matter with an aerodynamic diameter < 4 μg/m^3; $PM_{2.5}$ – particulate matter with an aerodynamic diameter < 2.5 μg/m^3; PM_1 – particulate matter with an aerodynamic diameter < 1 μg/m^3; UFP – ultrafine particles; $^{\omega}$ - *n* = 40; TVOC – total volatile organic compounds; ppb – parts per billion; CO_2 – carbon dioxide; ppm – parts per million; CO – carbon monoxide; NO_2 – nitrogen dioxide; HCHO – formaldehyde.

4.4.1 Concentrations of indoor air pollutants related to house characteristics

Independent samples t-tests and one-way analysis of variance (ANOVA) were conducted to determine if selected house characteristics influenced concentrations of indoor air pollutants.

Whilst a number of significant relationships were observed between some pollutants with several house characteristics, the age of the home, type of cooking appliances used, use of a cooking extractor fan, type of floor coverings, and the proximity of the home to a major roadway were not associated with the concentrations of any of the studied pollutants.

Furthermore, although all concentrations of gaseous pollutants other than HCHO were observed to be higher if a garage was reported to be attached to the home, none of these concentration differences were statistically significant.

Further relationships between indoor pollutants and household characteristics are summarised in Table 4.3 and 4.4.

Table 4. 3 Household characteristics and their impact on concentrations of indoor gaseous pollutants (TVOC, CO_2, CO, NO_2, HCHO).

Characteristic	n (%)	TVOC (ppb) mean ± SD	CO_2 (ppm) mean ± SD	CO (ppm) mean ± SD	NO_2 (ppm) mean ± SD	HCHO (µg/m^3) mean ± SD
Age of home						
<10 years	26 (23.4)	480.22 ± 442.78	474.98 ± 144.34	0.93 ± 0.14	0.15 ± 0.02	16.46 ± 5.19
>10 years	83 (74.8)	382.36 ± 191.36	471.44 ± 192.14	0.94 ± 0.15	0.16 ± 0.03	15.62 ± 4.78
p-value		0.292	0.933	0.795	0.504	0.456
No. of occupants						
1-2	43 (38.7)	346.83 ± 149.44	401.69 ± 138.30	0.92 ± 0.18	0.15 ± 0.02	15.92 ± 4.61
3+	66 (59.4)	447.51 ± 330.39	522.06 ± 191.97	0.95 ± 0.11	0.16 ± 0.03	15.80 ± 5.08
p-value		***0.039***	***< 0.001***	0.205	0.769	0.901
Type of heating						
Reverse cycle A/C	46 (41.4)	382.13 ± 165.55	420.96 ± 149.03	0.93 ± 0.12	0.15 ± 0.02	15.42 ± 3.53
Gas, electric, oil	28 (25.2)	556.72 ± 455.52	616.19 ± 206. 19	0.96 ± 0.13	0.16 ± 0.04	15.62 ± 6.63
Combination	31 (27.9)	300.28 ± 82.75	425.51 ± 146.34	0.94 ± 0.19	0.15 ± 0.02	17.03 ± 4.82
p-value		***0.002***	***< 0.001***	0.678	**0.054**	0.379
Type of cooling						
A/C	45 (40.5)	415.50 ± 217.26	486.06 ± 180.94	0.92 ± 0.10	0.15 ± 0.02	15.58 ± 4.34
Fans only	10 (9.0)	383.30 ± 221.76	665.36 ± 249.33	1.15 ± 0.24	0.17 ± 0.06	16.11 ± 8.40
A/C + fans	50 (45.0)	414.04 ± 334.76	431.51 ± 140.61	0.91 ± 0.12	0.15 ± 0.02	16.31 ± 4.54
p-value		0.945	***< 0.001***	***< 0.001***	**0.058**	0.782
Cleaning frequency						
Several times p/w	77 (69.4)	405.97 ± 295.22	476.59 ± 192.06	0.94 ± 0.16	0.16 ± 0.03	16.25 ± 4.94
Irregularly	31 (27.9)	407.53 ± 224.75	461.37 ± 157.44	0.92 ± 0.10	0.15 ± 0.02	14.58 ± 4.57
p-value		0.979	0.702	0.563	0.184	0.135

Floor coverings						
Carpet, linoleum	29 (26.1)	393.56 ± 161.18	497.45 ± 156.64	0.96 ± 0.11	0.14 ± 0.02	16.42 ± 4.47
Ceramic, stone, concrete	30 (27.0)	427.82 ± 424.08	460.26 ± 158.81	0.92 ± 0.14	0.16 ± 0.02	15.78 ± 4.13
Wood	50 (45.0)	399.82 ± 208.71	464.02 ± 208.76	0.94 ± 0.17	0.16 ± 0.03	15.54 ± 5.56
p-value		0.877	0.680	0.588	**0.058**	0.769
Cooking appliances						
Gas	25 (22.5)	458.53 ± 268.45	479.61 ± 161.68	0.95 ± 0.11	0.14 ± 0.01	16.65 ± 6.52
Electric	20 (18.0)	329.48 ± 95.62	476.47 ± 186.67	0.90 ± 0.12	0.15 ± 0.02	16.95 ± 4.80
Both	63 (56.8)	414.89 ± 312.15	466.63 ± 190.07	0.94 ± 0.16	0.16 ±0.03	15.18 ± 4.87
p-value		0.296	0.950	0.529	0.104	0.270
Use of cooking extractor fan						
Always/usually	97 (87.4)	411.82 ± 283.40	477.21 ± 187.12	0.93 ± 0.12	0.15 ± 0.03	15.92 ± 4.85
Never	12 (10.9)	360.34 ± 192.19	434.61 ± 125.91	0.98 ± 0.25	0.16 ± 0.02	15.20 ± 5.33
p-value		0.543	0.446	0.285	0.872	0.660
Distance from major roadway						
<300 m	53 (47.7)	445.71 ± 357.22	454.17 ± 173.95	0.93 ± 0.11	0.15 ± 0.02	15.07 ± 4.80
>300 m	53 (47.7)	375.05 ± 160.97	494.73 ± 188.82	0.95 ± 0.17	0.16 ± 0.03	16.47 ± 5.01
p-value		0.206	0.265	0.484	0.790	0.169

* *p* – value for independent samples t-test for two categories or ANOVA for 3+ categories.

n – number; TVOC – total volatile organic compounds; ppb – parts per billion; CO_2 – carbon dioxide; ppm – parts per million; CO – carbon monoxide; NO_2 – nitrogen dioxide; HCHO – formaldehyde; $\mu g/m^3$- micrograms per cubic metre; SD – standard deviation; A/C – air conditioning.

Table 4. 4 Household characteristics and their impact on concentrations of indoor PM (TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP).

Characteristic	n (%)	TPM (µg/m³) mean ± SD	PM_{10} (µg/m³) mean ± SD	PM_4 (µg/m³) mean ± SD	$PM_{2.5}$ (µg/m³) mean ± SD	PM_1 (µg/m³) mean ± SD	UFPω (particles/cm³) mean ± SD
Age of home							
<10 years	26 (23.4)	20.79 ± 16.68	17.89 ± 16.52	16.47 ± 16.17	15.84 ± 16.01	15.42 ± 16.02	10320 ± 6756
>10 years	83 (74.8)	21.36 ± 24.19	19.39 ± 23.72	17.88 ± 23.44	17.48 ± 23.35	16.96 ± 23.20	10905 ± 8854
p-value		0.924	0.797	0.806	0.775	0.787	0.861
No. of occupants							
1-2	43 (38.7)	18.92 ± 27.44	17.10 ± 26.83	15.79 ± 26.59	15.52 ± 26.55	15.02 ±26.46	10375 ± 10072
3+	66 (59.4)	22.96 ± 18.54	20.56 ± 18.24	18.94 ± 17.91	18.34 ± 17.78	17.84 ± 17.60	10881 ± 7403
p-value		0.410	0.475	0.509	0.554	0.551	0.795
Type of heating							
Reverse cycle A/C	46 (41.4)	20.39 ± 15.04	17.69 ± 14.37	16.03 ± 13.92	15.61 ± 13.66	15.14 ± 13.55	10759 ± 8053
Gas, electric, oil	28 (25.2)	16.43 ± 8.75	14.74 ± 8.42	13.21 ± 8.07	12.74 ± 7.94	12.30 ± 7.81	10878 ± 9043
Combination	31 (27.9)	27.00 ± 35.54	25.26 ± 35.47	24.00 ± 35.13	23.48 ± 35.12	22.92 ± 34.95	8074 ± 7090
p-value		0.247	0.223	0.192	0.194	0.197	0.766
Type of cooling							
A/C	45 (40.5)	15.25 ± 9.51	13.84 ± 9.16	12.35 ± 8.43	11.97 ± 8.21	11.52 ± 7.92	11162 ± 8465
Fans only	10 (9.0)	38.50 ± 51.64	36.62 ± 50.00	34.88 ± 49.88	34.38 ± 50.02	34.00 ± 49.76	8475 ± 4946
A/C + fans	50 (45.0)	23.02 ± 21.07	20.13 ± 20.86	18.65 ± 20.56	18.13 ± 20.41	17.61 ± 20.30	11824 ± 9019
p-value		***0.030***	***0.036***	***0.035***	***0.036***	***0.034***	0.753
Cleaning frequency							
Several times p/w	77 (69.4)	23.03 ± 25.58	20.98 ± 25.30	19.52 ± 24.99	19.03 ± 24.92	18.54 ± 24.76	13119 ± 9049
Irregularly	31 (27.9)	15.95 ± 9.84	13.45 ± 7.92	11.86 ± 7.38	11.50 ± 7.12	10.95 ± 7.16	6896 ± 4648
p-value		0.210	0.175	0.162	0.167	0.162	***0.008***

Floor coverings							
Carpet, linoleum	29 (26.1)	13.80 ± 8.10	12.68 ± 7.67	11.42 ± 6.97	11.05 ± 6.81	10.53 ± 6.78	8353 ± 8527
Ceramic, stone, concrete	30 (27.0)	21.67 ± 16.34	18.92 ± 15.80	17.25 ± 15.50	16.88 ± 15.25	16.33 ± 15.20	12490 ± 6338
Wood	50 (45.0)	24.31 ± 28.79	21.84 ± 28.32	20.36 ± 28.05	19.82 ± 28.01	19.36 ± 27.82	12251 ± 9261
p-value		0.228	0.327	0.335	0.346	0.336	0.327
Cooking appliances							
Gas	25 (22.5)	18.47 ± 9.93	16.10 ± 9.02	14.63 ± 8.47	13.89 ± 8.39	13.89 ± 8.39	8409 ± 6577
Electric	20 (18.0)	11.67 ± 6.19	10.93 ± 5.69	9.86 ± 5.52	9.64 ± 5.21	9.14 ± 4.94	7946 ± 5067
Both	63 (56.8)	25.07 ± 27.70	22.41 ± 27.31	20.80 ± 27.04	20.37 ± 26.95	19.80 ± 26.83	14048 ± 9769
p-value		0.108	0.185	0.204	0.203	0.211	**0.093**
Use of cooking extractor fan							
Always/usually	97 (87.4)	20.39 ± 17.32	18.20 ± 17.07	16.67 ± 16.74	16.17 ± 16.58	15.68 ± 16.43	11499 ± 8255
Never	12 (10.9)	27.90 ± 48.88	25.80 ± 47.46	24.70 ± 47.08	24.60 ± 47.07	24.00 ± 46.96	3957 ± 2705
p-value		0.641	0.627	0.605	0.587	0.591	**0.080**
Distance from major roadway							
<300 m	53 (47.7)	18.90 ± 12.34	16.54 ± 12.10	14.98 ± 11.82	14.54 ±11.68	13.95 ±11.71	10424 ± 8183
>300 m	53 (47.7)	23.87 ± 29.62	21.93 ± 29.15	20.50 ± 28.81	20.02 ± 28.80	19.59 ±28.50	11045 ± 8735
p-value		0.307	0.264	0.246	0.248	0.232	0.827

* *p* – value for independent samples t-test for two categories or ANOVA for 3+ categories.

n – number; $^{\omega}$ - n = 40; SD – standard deviation; TPM – total particulate matter; $\mu g/m^3$ micrograms per cubic metre; PM_{10} – particulate matter with an aerodynamic diameter < 10 $\mu g/m^3$; PM_4 – particulate matter with an aerodynamic diameter < 4 $\mu g/m^3$; $PM_{2.5}$ – particulate matter with an aerodynamic diameter < 2.5 $\mu g/m^3$; PM_1 – particulate matter with an aerodynamic diameter < 1 $\mu g/m^3$; UFP – particles with an aerodynamic diameter < 0.1 $\mu g/m^3$; particles/cm^3 – number of particles per cubic metre; SD – standard deviation; A/C – air conditioning.

4.4.2 Indoor air pollutant concentrations and ancillary variables

Bivariate analysis using Pearson's correlation coefficient (r) showed that 24-hour temperature was negatively associated with the 24-hour concentration of TPM (r = -0.18 p = 0.086), PM_{10} (r = -0.21, p = 0.050), PM_4 (r = -0.212, p = 0.047), $PM_{2.5}$ (r = -0.215, p = 0.044), PM_1 (r = -0.215, p =0.044), CO_2 (r = -0.248, p = 0.010) and CO concentrations (r = -0.288, p = 0.003). This finding suggests that higher concentrations of these indoor air pollutants are associated with lower indoor temperatures, however the strength of the association is weak.

Conversely, significant positive associations were demonstrated between 24-hour temperature and UFP (r = 0.321, p =0.043) and HCHO (r = 0.398, p < 0.001), indicating higher UFP and HCHO concentrations were associated with higher indoor temperatures. No relationship was noted between 24-hour indoor room temperature with TVOC or NO_2.

Similarly, indoor concentrations of NO_2 (r = -0.204, p =0.036) and HCHO (r = -0.176, p = 0.083) were found to be negatively associated with indoor relative humidity, although the strength of the association was also weak. No relationship was observed between relative humidity and any other indoor pollutants.

4.5 Clinical characteristics

4.5.1 Blood pressure

Blood pressure over 24-hours, daytime and nighttime, along with seated clinic BP were all within guideline targets set by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (AHF) (Table 2.2 and 2.3). Within the study population, 91.9% (n = 102) and 93.7% (n = 104) of participants recorded 24-hour systolic and diastolic BP below the AHF guidelines of < 130 mmHg and < 80 mmHg, respectively. Similar results were shown for daytime (87.4%; n = 97) and nighttime (90.1%; n = 100) systolic BP, and daytime (93.7%; n = 104) and nighttime (92.8%; n = 103) diastolic BP when compared to AHF guideline targets. Whilst clinic taken blood pressure can be subject to circumstance related variations, similar findings were noted to equivalent ambulatory daytime blood pressure readings with 86.5% (n =

96) of systolic readings and 91.9% (n = 102) of diastolic readings being below the AHF daytime guidelines of < 135 mmHg and < 85 mmHg respectively.

Further blood pressure characteristics and component measures for all study participants are summarised at Table 4.5.

Table 4.5 Blood pressure, central hemodynamic and arterial stiffness characteristics of study participants.

	Clinic		Ambulatory blood pressure monitor					
			24-hour		Daytime (awake)		Nighttime (asleep)	
	Mean ± SD	min - max	Mean ± SD	min - max	Mean ± SD	min - max	Mean ± SD	min - max
Cardiovascular endpoints								
pSBP, mmHg	117.7 ± 13.7[¶]	89 - 149	115.5 ± 11.1	93 - 158	121.4 ± 11.6	101 - 167	103.2 ± 12.6	81 - 153
cSBP, mmHg	108.6 ± 11.0[ω]	88 - 137	108.0 ± 9.8	90 - 145	113.2 ± 10.2	96 - 153	97.9 ± 11.3	80 - 135
pDBP, mmHg	71.1 ± 8.8[¶]	55 - 90	69.2 ± 7.5	55 - 95	74.0 ± 7.9	58 - 100	58.9 ± 8.5	43 - 88
cDBP, mmHg	73.5 ± 8.4[ω]	57 - 94	70.7 ± 7.7	57 - 97	75.9 ± 7.7	60 - 102	60.2 ± 8.5	47 - 85
HR, bpm	61.8 ± 8.8[¶]	44 - 86	70.6 ± 7.7	51 - 88	74.4 ± 9.3	52 - 106	62.1 ± 8.7	45 - 91
Systolic dip, %			15.5 ± 5.5	-8.2 - 31.2				
Diastolic dip, %			21.1 ± 6.9	0.1 - 36.6				
cSys dip, %			14.0 ± 5.6	-8.4 - 28.7				
cDia dip, %			21.3 ± 6.8	0.0 - 36.6				
cAIx, %			38.3 ± 9.5	15 - 59	36.7 ± 10.4	11 - 61	41.6 ± 10.2	17 - 63
cAIx75, %	17.2 ± 10.9[ω]	-16 - 57	35.6 ± 10.0	10 - 54	36.0 ± 10.4	9 - 58	35.1 ± 11.7	7 - 61
cAP, mmHg	8.8 ± 4.6[ω]	-1 - 27	14.9 ± 4.2	5 - 25	14.4 ± 4.6	4 - 28	16.0 ± 4.8	5 - 28
cPP, mmHg	34.9 ± 6.0[ω]	25 - 58	37.5 ± 5.5	27 - 60	37.4 ± 5.7	27 - 61	37.7 ± 5.9	25 - 59
cMAP, mmHg	86.4 ± 9.4[ω]	68 - 110	84.2 ± 8.5	68 - 116	92.2 ± 8.5	77 - 126	74.7 ± 9.4	59 - 109
PWV[ω], m/s	7.0 ± 1.2	3.8 - 10.3						

n = 111; [¶] - this measurement is taken in a seated position after 5 minutes rest; [ω] – this measurement is taken in a supine position during pulse wave analysis.

4.5.2 Lipid profile

Although it is recognised that blood cholesterol generally rises with age, the Royal Australian College of General Practitioners (2019) (RACGP) recommends general guideline targets for several blood lipids outlined at Table 2.4.

In this study, mean levels of total cholesterol (TC; 5.1; SD = 1.0 mmol/L), high-density lipoprotein (HDL; 1.7; SD = 0.5 mmol/L) and triglycerides (TG; 1.0; SD = 0.6 mmol/L) were within target limits recommended by the RACGP. Low-density lipoprotein (LDL; 3.0; SD = 0.8 mmol/L) and non-HDL (3.4; SD = 0.9 mmol/L) were above the RACGP targets of < 2.0 mmol/L and < 2.5 mmol/L, respectively. Within the study population, 64.9% (*n* = 72) of participants had TC levels below the RACGP target of < 5.5 mmol/L. Higher percentages of the study population had HDL (92.8%; *n* = 103) and TG (91.0%; n = 101) levels within RACGP targets of > 1.0 mmol/L and < 2.0 mmol/L, respectively. Only 9.9% (*n* = 11) and 14.4% (*n* = 16) of the population achieved LDL and non-HDL levels below the recommended targets of < 2.0 mmol/L and < 2.5 mmol/L, respectively.

Mean concentrations of serum cholesterols for study participants is shown at Table 4.6.

Table 4.6 Mean serum cholesterol concentrations of study participants.

Lipid profile		
	Mean ± SD	**min - max**
TC, mmol/L	5.1 ± 1.0	2.6 - 7.7
HDL, mmol/L	1.7 ± 0.5	0.7 - 2.6
LDL, mmol/L	3.0 ± 0.8	0.6 - 5.0
non-HDL, mmol/L	3.4 ± 0.9	1.8 - 5.5
TC/HDL	3.2 ± 0.9	1.8 - 7.1
TG, mmol/L	1.0 ± 0.6	0.5 - 4.5

n = 111.

4.5.3 Glucose metabolism

Mean HbA1c (5.2; SD = 0.3 %) and fasting glucose concentrations (5.1; SD = 0.6 mmol/L) were also below guideline levels recommended by the RACGP (Table 2.5).

All participants (n = 111) were observed to have a HbA1c below the RACGP target of < 6.5%, and 77.5% (n = 86) of participants were within the category of 'diabetes unlikely' with fasting blood glucose levels of < 5.5 mmol/L. No participants in this study reported fasting blood glucose levels that would be considered diabetic according to RACGP advocated guidelines (Table 2.5).

Mean levels of fasting blood glucose and HbA1c for all participants is presented at Table 4.7.

Table 4.7 Mean serum levels of fasting glucose and HbA1c for all study participants.

Glucose profile		
	Mean ± SD	**min - max**
Fasting glucose, mmol/L	5.1 ± 0.6	3.8 - 6.8
HbA1c, %	5.2 ± 0.3	4.7 - 6.5

n = 111

4.5.4 Renal function

The mean albumin/creatinine ratio (ACR) for the study population was 1.4 (SD = 0.8) mg/mmol which is below both male and female target levels recommended by the RACGP (Table 2.6).

When the study population was re-analysed by gender, 94.9% of males and 88.9% of females were observed to have an ACR below recommended levels of < 2.5 mg/mmol and < 3.5 mg/mmol, respectively.

Mean urinary concentrations of albumin and creatinine along with the ACR is presented in Table 4.8.

Table 4.8 Renal function profile for all study participants.

Renal profile		
	Mean ± SD	**min - max**
ACR, mg/mmol	1.4 ± 0.8	0.3 - 4.1
Albumin, mg/L	7.7 ± 5.5	5.0 - 36.0
Creatinine, mmol/L	7.4 ± 5.5	1.5 - 21.9

n = 111.

4.5.5 Clinic blood pressure versus 24-hour ambulatory blood pressure measurements

In analysing ambulatory blood pressure (ABP) data, where a participant's measurements did not comply with validity criteria described at section 3.5.1.4, these readings were excluded from the statistical analysis.

Consistently higher mean daytime ambulatory pSBP, pDBP, cSBP and cDBP was recorded when compared with equivalent clinic BP (seated and supine). As would be expected, higher BP values were observed for both peripheral and central systolic and diastolic measurements during the daytime compared with the measurements taken at night. For both clinic measurements and ABP measurements, pSBP was continually higher than cSBP. This is in contrast to pDBP which was always lower than cDBP for both clinic measurements and ABP measurements.

Table 4.9 presents the results of paired samples t-tests for comparing seated and supine BP (taken during PWA), and daytime ABP measurements (used as the equivalent measure to seated and supine measurements). Measurements used for analysis were all peripheral measures of SBP and DBP.

A significant difference for both systolic and diastolic measurements was shown between daytime ABP measurements and clinic blood pressure (SYS: t [108] = 3.63; $p < 0.001$; DIA: t [108] = 2.47; $p = 0.015$), with higher systolic and diastolic measurements observed when BP was recorded by means of 24-hour ABPM compared to BP measured in a seated position, in a clinic setting.

A significant difference (t [108] = 3.03; $p = 0.003$) was also shown between daytime systolic ABP and supine pSBP although this difference was only marginally significant (t [108] = 1.73; $p = 0.087$) for pDBP. Again, higher systolic and diastolic measurements were observed when BP was recorded using 24-hour ABPM compared to BP measured in a supine position.

These results indicate that BP measurements undertaken over 24-hours are slightly, but significantly higher than the equivalent clinic measurements taken in a seated or supine position. No significant differences were found between seated and supine clinic BP measurements.

Table 4.9 Comparisons between 24-ambulatory (daytime) blood pressure and equivalent seated and supine clinic blood pressure measurements.

	Systolic blood pressure (mmHg)			**Diastolic blood pressure (mmHg)**		
	Daytime SBP	***Clinic SBP***	***Supine SBP***	***Daytime DBP***	***Clinic DBP***	***Supine DBP***
Mean ± SD	121.4 ± 11.6	117.7 ± 13.8	118.7 ± 12.1	74.0 ± 7.9	72.7 ± 8.8	73.0 ± 8.4
Mean difference*		3.76	2.77		1.34	1.08
(95% CI)		(1.71, 5.81)	(0.96, 4.58)		(0.27, 2.41)	(-0.16, 2.32)
p-value[#]		***< 0.001***	***0.003***		***0.015***	**0.087**
		Clinic SBP	***Supine SBP***		***Clinic DBP***	***Supine DBP***
Mean ± SD		117.7 ± 13.8	118.7 ± 12.1		72.7 ± 8.8	73.0 ± 8.4
Mean difference[&]			0.97			0.24
(95% CI)			(-0.44, 2.38)			(-0.79, 1.28)
p-value[#]			0.174			0.639

* Daytime BP – Clinic/Supine BP; [&] Clinic BP – Supine BP; [#] Paired samples t-test.

4.6 Bivariate analysis between indoor air pollutants and sub-clinical cardiometabolic risk factors

4.6.1 Blood pressure

No significant relationships were observed between any of the measured indoor air pollutants with measures of BP, other than a weak negative correlation between NO_2 with supine measures of pSBP (r = -0.224, p = 0.021), and cSBP (r = -0.235, p = 0.016).

4.6.2 Central hemodynamic indices and measures of arterial stiffness

This study showed a significant positive correlation between 24-hour (r = 0.237, p = 0.019), daytime (r = 0.214, p = 0.036) and nighttime (r = 0.226, p = 0.026) central AIx with HCHO exposure. Other than for nighttime AIx_{75} in which only a marginally significant relationship was established (r = 0.191, p = 0.061), the same positive and significant relationship was observed by both 24-hour (r = 0.234, p = 0.021) and daytime (r = 0.234, p = 0.021) AIx_{75}.

A significant correlation was also shown between NO_2 with nighttime cPP (r = -0.204, p = 0.039).

4.6.3 Lipid, glucose and renal biomarkers

HDL was shown to have a negative relationship with TVOC (r = -0.274, p = 0.005) and CO_2 (r = -0.415, $p < 0.001$), however with the removal of two outlying data points, this relationship was further strengthened (r = -0.484, $p < 0.001$). TC and CO_2 were also observed to have a significant negative relationship (r = -0.285, p = 0.003) and TVOC (r = 0.232, p = 0.017) and CO_2 (r = 0.249, p = 0.010) were found to have a statistically significant relationship with TC/HDL.

4.7 Associations between indoor air pollutants and sub-clinical cardiometabolic risk factors

Associations between indoor air pollutants and sub-clinical cardiometabolic risk factors were evaluated using multiple linear regression models. Regression models were adjusted using covariates identified from previously published literature of similar studies. Covariates included age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high) (R. D. Brook, Bard, et al., 2008; Z. Chen et al., 2016; Huxley et al., 2010; S. Rajkumar et al., 2018; C.-F. Wu et al., 2016; X. M. Wu et al., 2019; Young et al., 2019). The results of the linear regression analysis are reported by mean change in the outcome (dependent) variable with 95% confidence intervals for per IQR increase of exposure to each indoor air pollutant. Due to very large UFP concentration values compared to outcome values (e.g., AIx, AIx_{75} [%]), UFP concentrations were transformed using the decimal scaling normalisation method described in other published literature (Eesa A.S. & Arabo W.K., 2017; Folorunso et al., 2018; Magalhaes et al., 2018; Manimekalai & Kavitha, 2018) prior to the regression analyses. Using this method, UFP concentrations were divided by 10^3 to create a comparable measurement scale and enable meaningful, interpretable results. Similarly, TVOC and CO_2 concentrations and their respective IQR's were also scaled (TVOC by 10^2; CO_2 by 10) to evaluate the relationship with blood and urine markers at Tables 4.16, 4.17 and 4.18.

4.7.1 Gaseous pollutants with blood pressure

An interquartile range increase in exposure to NO_2 (IQR = 0.031 ppm) was associated with a significant decrease of 2.40 mmHg in 24-hour cSBP (95% CI: -4.74, -0.05; p = 0.045) and 2.10 mmHg in daytime cSBP (95% CI: -4.02, -0.17; p = 0.033). However, a non-significant decrease was observed with nighttime cSBP (-1.44 mmHg; 95% CI: -3.75, 0.87; p = 0.220). Twenty-four-hour pSBP (-2.32 mmHg; 95% CI: -4.95, 0.30; p = 0.081) and 24-hour cDBP (-1.67 mmHg; 95% CI: -3.62, -0.28; p = 0.092) showed similar reductions, although these results failed to achieve statistical significance at the 5% level.

Further associations between gaseous pollutants and measures of central and peripheral ambulatory blood pressure are summarized at Table 4.10.

4.7.2 PM with blood pressure

The study did not find any significant associations between any size fraction of PM and measures of central and peripheral blood pressure. These results are presented in Table 4.11.

Table 4.10 Mean changes (95% CI) in measures of blood pressure associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutants				
	TVOC; ppb (IQR = 124.7)	**HCHO; µg/m3** (IQR = 6.25)	**CO_2; ppm** (IQR = 291.8)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
24-hour SYS, mmHg	-0.12 (-1.25, 1.12)	1.46 (-4.18, 1.26)	-1.75 (-5.25, 1.75)	-0.12 (-2.20, 1.96)	**-2.32 (-4.95, 0.30)**
p-value	0.858	0.288	0.351	0.908	**0.081**
24-hour DIA, mmHg	0.00 (-0.87, 0.87)	-0.24 (-2.20, 1.72)	-1.46 (-4.08, 1.17)	-0.32 (-1.81, 1.17)	-1.57 (-3.46, 0.32)
p-value	0.950	0.806	0.247	0.672	0.103
cSYS BP, mmHg					
24-hour	-0.12 (-1.12, 1.00)	-1.06 (-3.5, 1.38)	-0.58 (-3.79, 2.63)	0.03 (-1.84, 1.89)	***-2.40 (-4.74, -0.05)***
p-value	0.904	0.391	0.741	0.976	***0.045***
Daytime	-0.62 (-1.37, 0.25)	-0.50 (-2.87, 1.85)	-1.46 (-4.38, 1.17)	0.00 (-1.79, 1.78)	***-2.10 (-4.02, -0.17)***
p-value	0.153	0.671	0.265	0.994	***0.033***
Nighttime	-0.62 (-1.62, 0.37)	-1.12 (-3.89, 1.64)	-0.29 (-2.92, 3.79)	-0.42 (-2.53, 1.68)	-1.44 (-3.75, 0.87)
p-value	0.213	0.421	0.809	0.693	0.220
cDIA BP, mmHg					
24-hour	0.00 (-0.87, 0.87)	-0.28 (-2.29, 1.74)	-1.17 (-4.08, 1.46)	-0.42 (-1.95, 1.11)	-1.67 (-3.62, 0.28)
p-value	0.993	0.786	0.333	0.587	0.092
Daytime	-0.37 (-1.12, 0.25)	0.1 (-1.87, 2.08)	-0.88 (-3.21, 1.46)	-0.05 (-1.56, 1.45)	-1.07 (-2.72, 0.58)
p-value	0.222	0.918	0.477	0.946	0.203
Nighttime	-0.37 (-1.25, 0.37)	-0.40 (-2.62, 1.82)	0.88 (-1.75, 3.50)	-0.08 (-1.77, 1.62)	-0.14 (-2.01, 1.74)
p-value	0.295	0.722	0.549	0.927	0.884
SYS DIP, %	0.37 (-0.37, 1.00)	0.60 (-0.98, 2.18)	-0.58 (-2.63, 1.75)	0.78 (-0.42, 1.98)	-0.90 (-2.45, 0.65)
p-value	0.341	0.450	0.648	0.200	0.252
DIA DIP, %	0.00 (-0.87, 0.87)	0.74 (-1.18, 2.67)	-0.58 (-3.21, 2.04)	0.76 (-0.73, 2.25)	-1.06 (-2.98, 0.85)

p-value	0.911	0.446	0.666	0.314	0.272
cSYS DIP, %	0.25 (-0.37, 1.00)	0.81 (-0.80, 2.41)	-0.58 (-2.92, 1.46)	0.81 (-0.43, 2.05)	-0.72 (-2.33, 0.90)
p-value	0.404	0.320	0.532	0.199	0.379
cDIA DIP, %	0.25 (-0.62, 1.12)	0.94 (-0.98, 2.85)	-0.88 (-3.50, 1.75)	0.53 (-0.96, 2.03)	-1.14 (-3.06, 0.78)
p-value	0.610	0.333	0.509	0.482	0.243

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor gaseous pollutants.

Table 4.11 Mean changes (95% CI) in measures of blood pressure associated with a one IQR increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP numbers.

	PM size fraction					
	TPM; µg/m³ (IQR=15)	**PM_{10}; µg/m³** (IQR=11)	**PM_4; µg/m³** (IQR=11)	**$PM_{2.5}$; µg/m³** (IQR=10.5)	**PM_1; µg/m³** (IQR=10.5)	**UFP¶; particles/cm³** (IQR=12.8)
24-hour SYS, mmHg	0.44 (-0.86, 1.74)	0.27 (-0.88, 1.44)	0.22 (-0.78, 1.21)	0.20 (-0.76, 1.16)	0.19 (-0.78, 1.14)	-1.86 (-8.23, 4.50)
p-value	0.499	0.637	0.667	0.680	0.700	0.552
24-hour DIA, mmHg	-0.06 (-1.04, 0.93)	-0.17 (-1.04, 0.72)	-0.15 (-0.90, 0.60)	-0.15 (-0.87, 0.57)	-0.15 (-0.87, 0.58)	1.77 (-3.58, 7.13)
p-value	0.913	0.708	0.691	0.682	0.678	0.501
cSYS BP, mmHg						
24-hour	0.30 (-0.86, 1.47)	0.14 (-0.90, 1.20)	-0.11 (-0.79, 1.01)	0.09 (-0.77, 0.96)	0.09 (-0.78, 0.96)	-1.33 (-6.85, 4.18)

p-value	0.603	0.777	0.808	0.829	0.837	0.622
Daytime	0.30 (-0.82, 1.42)	0.12 (-0.88, 1.12)	0.08 (-0.78, 0.94)	0.06 (-0.76, 0.89)	0.06 (-0.77, 0.89)	-3.15 (-7.83, 1.52)
p-value	0.604	0.817	0.861	0.873	0.882	0.179
Nighttime	-0.21 (-1.70, 1.26)	-0.27 (-1.61, 1.05)	-0.25 (-1.39, 0.89)	-0.24 (-1.33, 0.86)	-0.26 (-1.36, 0.84)	-1.13 (-7.68, 5.43)
p-value	0.774	0.683	0.667	0.664	0.634	0.728
cDIA BP, mmHg						
24-hour	-0.15 (-1.17, 0.87)	-0.26 (-1.17, 0.65)	-0.23 (-1.01, 0.55)	-0.23 (-0.98, 0.52)	-0.23 (-0.98, 0.52)	1.33 (-4.01, 6.69)
p-value	0.773	0.572	0.558	0.548	0.549	0.612
Daytime	-0.10 (-1.12, 0.90)	-0.23 (-1.14, 0.66)	-0.21 (-0.99, 0.56)	-0.21 (-0.96, 0.54)	-0.21 (-0.96, 0.54)	-0.52 (-5.09, 4.06)
p-value	0.833	0.601	0.585	0.575	0.578	0.818
Nighttime	-0.26 (-1.46, 0.96)	-0.26 (-1.35, 0.83)	-0.23 (-1.17, 0.70)	-0.23 (-1.12, 0.66)	-0.24 (-1.13, 0.66)	0.96 (-4.39, 6.30)
p-value	0.681	0.637	0.626	0.611	0.600	0.717
SYS DIP, %	0.28 (-0.56, 1.12)	0.23 (-0.52, 0.99)	0.20 (-0.45, 0.85)	0.19 (-0.43, 0.81)	0.20 (-0.42, 0.83)	-0.17 (-5.26, 4.93)
p-value	0.501	0.538	0.546	0.553	0.522	0.946
DIA DIP, %	0.28 (-0.74, 1.32)	0.20 (-0.73, 1.12)	0.16 (-0.63, 0.96)	0.16 (-0.60, 0.92)	0.17 (-0.59, 0.93)	-0.20 (-6.35, 5.93)
p-value	0.574	0.675	0.673	0.672	0.654	0.944
cSYS DIP, %	0.28 (-0.58, 1.14)	0.23 (-0.55, 1.01)	0.20 (-0.46, 0.86)	0.19 (-0.45, 0.82)	0.20 (-0.44, 0.84)	-0.63 (-5.88, 4.62)
p-value	0.520	0.546	0.554	0.561	0.533	0.807
cDIA DIP, %	0.20 (-0.86, 1.24)	0.10 (-0.84, 1.05)	0.09 (-0.73, 0.90)	0.08 (-0.69, 0.86)	0.09 (-0.68, 0.87)	-0.81 (-6.81, 5.20)
p-value	0.711	0.824	0.829	0.824	0.811	0.785

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor particulate matter concentrations. ¶ - UFP concentrations and IQR have been scaled by 10^3.

4.7.3 Gaseous pollutants with central hemodynamic indices and arterial stiffness

Whilst several gaseous pollutants were observed to significantly impact measures and correlates of arterial stiffness (cAIx, $cAIx_{75}$, cPP, PWV), these were mostly limited to volatile components. No relationships were shown between any of the measured gaseous pollutants with central hemodynamic indices.

Further relationships between measures of arterial stiffness and central hemodynamic indices with gaseous pollutants are summarized at Table 4.12 and 4.13.

4.7.4 PM with central hemodynamic indices and arterial stiffness

Significant relationships were demonstrated between UFP with measures and correlates of arterial stiffness including cAIx, $cAIx_{75}$ and 24-hour and daytime cPP (Table 4.13).

No relationships were observed between central hemodynamic and arterial stiffness measures and any other PM size fractions.

These results are summarized in Tables 4.14 and 4.15.

Table 4.12 Mean changes (95% CI) in hemodynamic measures of arterial stiffness associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutant				
	TVOC; ppb (IQR = 124.7)	**HCHO; μg/m³** (IQR = 6.25)	**CO_2; ppm** (IQR = 291.8)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
cAIx, %					
24-hour	***1.00 (0.25, 1.87)***	***2.37 (0.12, 4.61)***	**2.33 (-0.29, 5.25)**	0.74 (-1.01, 2.50)	0.03 (-1.92, 1.98)
p-value	***0.011***	***0.039***	**0.080**	0.403	0.977
Daytime	***1.25 (0.37, 2.12)***	**2.46 (-0.12, 5.04)**	**2.63 (-0.58, 5.84)**	0.70 (-1.32, 2.72)	0.32 (-1.92, 2.56)
p-value	***0.009***	**0.062**	**0.090**	0.492	0.776
Nighttime	***0.87 (0.12, 1.74)***	**2.25 (-0.14, 4.64)**	1.46 (-1.46, 4.38)	0.42 (-1.41, 2.26)	-0.74 (-2.76, 1.28)
p-value	***0.033***	**0.065**	0.324	0.647	0.471
$cAIx_{75}$, %					
24-hour	***0.87 (0.12, 1.74)***	***2.29 (0.01, 4.56)***	2.04 (-0.88, 4.67)	0.82 (-0.93, 2.58)	0.01 (-1.93, 1.96)
p-value	***0.028***	***0.049***	0.176	0.352	0.989
Daytime	***1.00 (0.12, 1.87)***	***2.51 (0.06, 4.96)***	2.04 (-0.88, 4.96)	0.67 (-1.24, 2.58)	0.16 (-1.96, 2.28)
p-value	***0.023***	***0.045***	0.187	0.489	0.883
Nighttime	**0.87 (0.00, 1.74)**	1.89 (-0.76, 4.54)	1.46 (-1.75, 4.67)	1.00 (-1.00, 2.99)	-0.29 (-2.51, 1.93)
p-value	**0.064**	0.163	0.395	0.323	0.796
PWV, m/s	0.00 (-0.12, 0.12)	-0.00 (-0.29, 0.28)	0.00 (-0.29, 0.29)	0.04 (-0.18, 0.26)	-0.13 (-0.37, 0.12)
p-value	0.560	0.980	0.897	0.721	0.299

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor gaseous pollutants.

Table 4.13 Mean changes (95% CI) in central hemodynamic measures associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutant				
	TVOC; ppb (IQR = 124.7)	**HCHO; μg/m³** (IQR = 6.25)	**CO_2; ppm** (IQR = 291.8)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
cAP, mmHg					
24-hour	0.25 (0.00, 0.62)	0.51 (-0.46, 1.49)	0.58 (-0.58, 1.75)	0.20 (-0.06, 0.96)	-0.34 (-1.18, 0.50)
p-value	0.104	0.297	0.284	0.602	0.423
Daytime	0.37 (-0.12, 0.75)	0.51 (-0.58, 1.59)	0.58 (-0.88, 2.04)	0.29 (-0.56, 1.14)	-0.24 (-1.18, 0.70)
p-value	0.101	0.359	0.401	0.494	0.608
Nighttime	0.25 (-0.12, 0.62)	0.37 (-0.76, 1.50)	0.58 (-0.88, 1.75)	0.02 (-0.83, 0.88)	-0.72 (-1.65, 0.22)
p-value	0.251	0.521	0.477	0.957	0.132
cPP, mmHg					
24-hour	-0.12 (-0.62, 0.25)	-0.74 (-2.01, 0.52)	-0.58 (-2.04, 0.88)	-0.08 (-1.05, 0.89)	***-1.07 (-2.12, -0.02)***
p-value	0.455	0.244	0.430	0.867	***0.046***
Daytime	-0.12 (-0.62, 0.25)	-0.57 (-1.86, 0.72)	-0.88 (-2.33, 0.58)	0.02 (-0.97, 1.01)	**-1.05 (-2.12, 0.02)**
p-value	0.457	0.385	0.286	0.969	**0.053**
Nighttime	-0.25 (-0.75, 0.25)	-0.76 (-2.22, 0.71)	-0.29 (-2.04, 1.46)	-0.37 (-1.48, 0.75)	***-1.28 (-2.49, -0.07)***
p-value	0.428	0.307	0.684	0.514	***0.038***
cMAP, mmHg					
24-hour	-0.50 (-1.25, 0.25)	-0.22 (-2.36, 1.92)	-0.58 (-3.21, 2.04)	-0.08 (-1.70, 1.55)	-1.26 (-3.03, 0.52)
p-value	0.233	0.837	0.687	0.926	0.163
Daytime	-0.37 (-1.12, 0.37)	-0.13 (-2.26, 2.01)	-1.17 (-3.79, 1.46)	0.10 (-1.52, 1.73)	-1.39 (-3.17, 0.38)
p-value	0.259	0.905	0.387	0.901	0.123
Nighttime	-0.50 (-1.37, 0.37)	-0.82 (-3.28, 1.64)	0.88 (-2.04, 3.79)	0.02 (-1.86, 0.19)	-0.55 (-2.62, 1.52)

p-value	0.303	0.508	0.557	0.987	0.599

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor gaseous pollutants.

Table 4.14 Mean changes (95% CI) in hemodynamic measures of arterial stiffness measures associated with a one interquartile range (IQR) increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP numbers.

	PM size fraction					
	TPM; µg/m³ (IQR=15)	**PM_{10}; µg/m³** (IQR=13)	**PM_4; µg/m³** (IQR=11)	**$PM_{2.5}$; µg/m³** (IQR=10.5)	**PM_1; µg/m³** (IQR=10.5)	**UFP¶; particles/cm³** (IQR=12.8)
cAIx, %						
24-hour	-0.15 (-1.38, 1.08)	-0.10 (-1.20, 1.00)	-0.10 (-1.06, 0.85)	0.09 (-1.01, 0.82)	-0.08 (-1.01, 0.83)	***5.38 (0.19, 10.56)***
p-value	0.814	0.851	0.830	0.838	0.851	***0.043***
Daytime	-0.03 (-1.44, 1.38)	0.01 (-1.26, 1.29)	-0.01 (-1.1, 1.08)	0.01 (-1.06, 1.03)	-0.01 (-1.06, 1.05)	**5.24 (-0.90, 11.37)**
p-value	0.963	0.988	0.985	0.976	0.987	**0.092**
Nighttime	-0.28 (-1.58, 0.99)	-0.32 (-1.47, 0.83)	-0.29 (-1.28, 0.70)	0.25 (-1.20, 0.69)	-0.24 (-1.20, 0.71)	***6.10 (1.45, 10.78)***
p-value	0.651	0.583	0.574	0.599	0.611	***0.012***
$cAIx_{75}$, %						
24-hour	-0.48 (-1.70, 0.75)	-0.35 (-1.46, 0.74)	-0.31 (-1.24, 0.64)	-0.28 (-1.19, 0.62)	-0.27 (-1.19, 0.63)	***6.14 (1.33, 10.96)***
p-value	0.443	0.526	0.519	0.537	0.548	***0.014***
Daytime	-0.48 (-1.80, 0.84)	-0.32 (-1.51, 0.86)	-0.29 (-1.31, 0.73)	-0.27 (-1.25, 0.70)	-0.27 (-1.25, 0.71)	***5.84 (0.27, 11.42)***
p-value	0.475	0.584	0.571	0.579	0.587	***0.041***
Nighttime	-0.48 (-1.89, 0.93)	-0.46 (-1.73, 0.81)	-0.40 (-1.48, 0.69)	-0.36 (-1.40, 0.68)	-0.36 (-1.41, 0.69)	***7.21 (2.46, 11.97)***
p-value	0.498	0.475	0.469	0.496	0.505	***0.004***

PWV, m/s	-0.02 (-0.16, 0.14)	-0.01 (-0.14, 0.13)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.10)	-0.01 (-0.12, 0.10)	**-0.40 (-0.86, 0.08)**
p-value	0.852	0.898	0.918	0.913	0.907	**0.095**

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor particulate matter concentrations. ¶ - UFP concentrations and IQR have been scaled by 10^3.

Table 4.15 Mean changes (95% CI) in central hemodynamic measures associated with a one interquartile range (IQR) increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP numbers.

	PM size fraction					
	TPM; µg/m^3 (IQR=15)	**PM_{10}; µg/m^3** (IQR=13)	**PM_4; µg/m^3** (IQR=11)	**$PM_{2.5}$; µg/m^3** (IQR=10.5)	**PM_1; µg/m^3** (IQR=10.5)	**UFP¶; particles/cm^3** (IQR=12.8)
cAP, mmHg						
24-hour	0.03 (-0.50, 0.57)	0.04 (-0.44, 0.52)	0.02 (-0.38, 0.44)	0.02 (-0.37, 0.42)	0.02 (-0.38, 0.42)	1.16 (-0.98, 3.30)
p-value	0.903	0.886	0.907	0.904	0.905	0.278
Daytime	0.12 (-0.48, 0.74)	0.13 (-0.42, 0.69)	0.10 (-0.36, 0.57)	0.09 (-0.36, 0.55)	0.09 (-0.36, 0.56)	1.00 (-1.46, 3.46)
p-value	0.678	0.631	0.661	0.672	0.671	0.416
Nighttime	0.08 (-0.68, 0.52)	-0.12 (-0.65, 0.42)	-0.11 (-0.56, 0.35)	-0.09 (-0.54, 0.35)	-0.09 (-0.55, 0.35)	1.60 (-0.49, 3.69)
p-value	0.810	0.667	0.652	0.676	0.668	0.127
cPP, mmHg						
24-hour	0.24 (-0.44, 0.92)	0.21 (-0.40, 0.81)	0.16 (-0.36, 0.68)	0.16 (-0.35, 0.66)	0.15 (-0.36, 0.65)	***-2.28 (-4.53, -0.01)***
p-value	0.478	0.507	0.536	0.534	0.558	***0.049***
Daytime	0.39 (-0.28, 1.08)	0.34 (-0.27, 0.95)	0.28 (-0.25, 0.80)	0.26 (-0.24, 0.77)	0.26 (-0.25, 0.77)	***-2.64 (-4.89, -0.37)***
p-value	0.249	0.271	0.298	0.300	0.311	***0.024***
Nighttime	0.03 (-0.76, 0.82)	-0.01 (-0.73, 0.70)	-0.02 (-0.64, 0.59)	-0.01 (-0.60, 0.58)	-0.03 (-0.62, 0.57)	-2.29 (-5.30, 0.72)

p-value	0.947	0.959	0.947	0.967	0.923	0.130
cMAP, mmHg						
24-hour	0.12 (-1.2, 0.98)	-0.02 (-1.21, 0.75)	-0.21 (-1.04, 0.64)	-0.20 (-1.01, 0.60)	-0.21 (-1.02, 0.61)	-0.73 (-5.40, 3.93)
p-value	0.838	0.654	0.626	0.617	0.611	0.749
Daytime	-0.02 (-1.06, 1.04)	-0.16 (-1.09, 0.79)	-0.14 (-0.95, 0.66)	-0.14 (-0.91, 0.63)	-0.15 (-0.92, 0.64)	-1.20 (-5.93, 3.51)
p-value	0.973	0.753	0.726	0.719	0.718	0.604
Nighttime	-0.32 (-1.65, 1.00)	-0.33 (-1.53, 0.87)	-0.30 (-1.33, 0.74)	-0.29 (-1.28, 0.69)	-0.30 (-1.30, 0.69)	0.46 (-5.70, 6.62)
p-value	0.633	0.579	0.568	0.561	0.543	0.879

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor particulate matter concentrations. ¶ - UFP concentrations and IQR have been scaled by 10^3.

4.7.5 Gaseous pollutants with lipid, glucose and renal biomarkers

Exposure to CO_2 appeared to have a significant impact on lipid biomarkers TC and HDL, with reductions observed as CO_2 increased. In contrast, HbA1c was shown to rise with a corresponding IQR increase in CO_2.

Further associations between lipid, glucose and renal biomarkers with indoor gaseous pollutants estimated per IQR change are presented at Tables 4.16, 4.17 and 4.18.

4.7.6 PM with lipid, glucose and renal biomarkers

There were no observed associations between any size fraction of PM with lipid, glucose or renal biomarkers. These results are summarized at Tables 4.19, 4.20 and 4.21.

Table 4.16 Mean changes (95% CI) in lipid biomarkers associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutant				
	TVOC[‡]; ppb (IQR = 1.247)	**HCHO; µg/m³** (IQR = 6.25)	**CO_2[§]; ppm** (IQR = 29.18)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
TC, mmol/L	-0.05 (-0.14, 0.04)	0.01 (-0.23, 0.26)	***-0.39 (-0.69, -0.10)***	-0.02 (-0.21, 0.16)	-0.17 (-0.38, 0.03)
p-value	0.263	0.919	***0.009***	0.799	0.099
HDL, mmol/L	**-0.04 (-0.08, 0.00)**	-0.05 (-0.16, 0.06)	***-0.24 (-0.37, -0.12)***	-0.04 (-0.12, 0.05)	-0.03 (-0.12, 0.06)
p-value	**0.062**	0.355	***<0.001***	0.376	0.518
LDL, mmol/L	-0.02 (-0.10, 0.05)	0.02 (-0.18, 0.23)	-0.13 (-0.38, 0.11)	0.03 (-0.12, 0.19)	-0.12 (-0.30, 0.04)
p-value	0.504	0.817	0.285	0.690	0.148
non-HDL, mmHg	-0.01 (-0.09, 0.06)	0.06 (-0.15, 0.28)	-0.15 (-0.41, 0.11)	0.01 (-0.15, 0.18)	-0.14 (-0.32, 0.03)
p-value	0.737	0.565	0.253	0.868	0.111
TC/HDL	**0.07 (-0.01, 0.14)**	0.11 (-0.11, 0.32)	***0.28 (0.01, 0.54)***	0.04 (-0.12, 0.21)	-0.06 (-0.25, 0.12)
p-value	**0.086**	0.318	***0.040***	0.616	0.505
TG, mmol/L	0.02 (-0.04, 0.08)	0.08 (-0.08, 0.24)	-0.03 (-0.22, 0.16)	-0.04 (-0.15, 0.08)	-0.05 (-0.18, 0.08)
p-value	0.469	0.294	0.773	0.554	0.428

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor gaseous pollutants. [‡] – TVOC concentrations and IQR have been scaled by 10^2; [§] – CO^2 concentrations and IQR have been scaled by 10.

Table 4.17 Mean changes (95% CI) in glucose biomarkers associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutant				
	TVOC‡; ppb (IQR = 1.247)	**HCHO; µg/m³** (IQR = 6.25)	**CO_2§; ppm** (IQR = 29.18)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
Fasting glucose, mmol/L	-0.01 (-0.06, 0.04)	0.04 (-0.09, 0.18)	-0.12 (-0.29, 0.05)	***-0.11 (-0.21, 0.00)***	-0.08 (-0.20, 0.04)
p-value	0.650	0.510	0.161	***0.043***	0.195
HbA1c, %	0.00 (-0.02, 0.02)	0.01 (-0.06, 0.08)	***0.08 (0.00, 0.17)***	0.03 (-0.02, 0.08)	-0.03 (-0.09, 0.02)
p-value	0.972	0.729	***0.041***	0.271	0.236

Table 4.18 Mean changes (95% CI) in renal function biomarkers associated with a one IQR increase in TVOC, HCHO, CO_2, CO and NO_2.

	Gaseous pollutant				
	TVOC‡; ppb (IQR = 1.247)	**HCHO; µg/m³** (IQR = 6.25)	**CO_2§; ppm** (IQR = 29.18)	**CO; ppm** (IQR = 0.15)	**NO_2; ppm** (IQR = 0.031)
ACR, mg/mmol	-0.02 (-0.09, 0.05)	0.01 (-0.19, 0.21)	**-0.22 (-0.47, 0.03)**	-0.10 (-0.25, 0.06)	-0.05 (-0.22, 0.12)
p-value	0.558	0.926	**0.087**	0.207	0.577
Albumin, mg/L	-0.26 (-0.81, 0.30)	**1.39 (-0.17, 2.95)**	-1.42 (-3.34, 0.49)	-0.29 (-1.49, 0.92)	0.16 (-1.17, 1.48)
p-value	0.366	**0.080**	0.144	0.636	0.817
Creatinine, mmol/L	-0.20 (-0.70, 0.30)	0.39 (-1.03, 1.81)	-0.11 (-1.85, 1.63)	0.25 (-0.83, 1.32)	0.45 (-0.73, 1.64)
p-value	0.437	0.586	0.902	0.454	0.450

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor gaseous pollutants. ‡ – TVOC concentrations and IQR have been scaled by 10^2; § – CO^2 concentrations and IQR have been scaled by 10.

Table 4.19 Mean changes (95% CI) in lipid biomarkers associated with a one IQR increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP.

	PM size fraction

	TPM; μg/m^3 (IQR=15)	PM_{10}; μg/m^3 (IQR=13)	PM_4; μg/m^3 (IQR=11)	$PM_{2.5}$; μg/m^3 (IQR=10.5)	PM_1; μg/m^3 (IQR=10.5)	UFP[¶]; particles/cm^3 (IQR=12.8)
TC, mmol/L	0.00 (-0.12, 0.14)	-0.01 (-0.13, 0.10)	-0.01 (-0.11, 0.08)	-0.01 (-0.10, 0.07)	-0.01 (-0.10, 0.07)	-0.15 (-0.68, 0.37)
p-value	0.964	0.843	0.761	0.760	0.754	0.551
HDL, mmol/L	-0.02 (-0.08, 0.04)	-0.03 (-0.08, 0.03)	-0.02 (-0.07, 0.02)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	-0.10 (-0.33, 0.13)
p-value	0.528	0.425	0.403	0.414	0.397	0.368
LDL, mmol/L	0.04 (-0.06, 0.15)	0.03 (-0.06, 0.13)	0.02 (-0.06, 0.11)	0.02 (-0.05, 0.10)	0.02 (-0.05, 0.10)	0.02 (-0.40, 0.46)
p-value	0.417	0.509	0.573	0.585	0.588	0.884
non-HDL, mmol/L	0.02 (-0.09, 0.14)	-0.01 (-0.09, 0.10)	0.00 (-0.08, 0.09)	0.00 (-0.07, 0.08)	0.00 (-0.07, 0.08)	-0.05 (-0.51, 0.41)
p-value	0.700	0.845	0.924	0.934	0.928	0.822
TC/HDL	0.03 (-0.09, 0.15)	0.03 (-0.09, 0.13)	0.02 (-0.08, 0.11)	0.02 (-0.07, 0.10)	0.02 (-0.07, 0.10)	0.05 (-0.50, 0.60)
p-value	0.682	0.678	0.711	0.716	0.706	0.833
TG, mmol/L	-0.06 (-0.14, 0.03)	-0.05 (-0.13, 0.03)	-0.04 (-0.11, 0.02)	-0.04 (-0.10, 0.02)	-0.04 (-0.10, 0.02)	-0.19 (-0.52, 0.13)
p-value	0.198	0.183	0.182	0.186	0.194	0.232

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor particulate matter concentrations. [¶] – UFP concentrations have been scaled by 10^3.

Table 4.20 Mean changes (95% CI) in glucose biomarkers associated with a one IQR increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP.

	PM size fraction					
	TPM; μg/m^3	**PM_{10}; μg/m^3**	**PM_4; μg/m^3**	**$PM_{2.5}$; μg/m^3**	**PM_1; μg/m^3**	**UFP[¶]; particles/cm^3**

	(IQR=15)	(IQR=13)	(IQR=11)	(IQR=10.5)	(IQR=10.5)	(IQR=12.8)
Fasting glucose, mmol/L	-0.06 (-0.14, 0.02)	-0.05 (-0.12, 0.01)	-0.04 (-0.10, 0.01)	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)	-0.13 (-0.36, 0.10)
p-value	0.122	0.131	0.131	0.126	0.127	0.284
HbA1c, %	0.00 (-0.04, 0.03)	0.00 (-0.04, 0.03)	0.00 (-0.03, 0.02)	0.00 (-0.03, 0.02)	0.00 (-0.03, 0.02)	0.05 (-0.09, 0.20)
p-value	0.795	0.907	0.891	0.894	0.892	0.469

Table 4.21 Mean changes (95% CI) in renal function biomarkers associated with a one IQR increase in TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1 and UFP.

	PM size fraction					
	TPM; µg/m^3	**PM_{10}; µg/m^3**	**PM_4; µg/m^3**	**$PM_{2.5}$; µg/m^3**	**PM_1; µg/m^3**	**UFP[¶]; particles/cm^3**
	(IQR=15)	(IQR=13)	(IQR=11)	(IQR=10.5)	(IQR=10.5)	(IQR=12.8)
ACR, mg/mmol	0.03 (-0.06, 0.12)	0.03 (-0.06, 0.10)	0.02 (-0.06, 0.09)	0.02 (-0.05, 0.08)	0.02 (-0.05, 0.08)	**-0.38 (-0.79, 0.04)**
p-value	0.579	0.617	0.602	0.612	0.596	**0.071**
Albumin, mg/L	-0.36 (-0.86, 0.12)	-0.34 (-0.77, 0.10)	-0.29 (-0.66, 0.09)	-0.27 (-0.63, 0.08)	-0.27 (-0.63, 0.09)	-1.78 (-4.39, 0.83)
p-value	0.136	0.129	0.132	0.132	0.142	0.175
Creatinine, mmol/L	-0.44 (-1.2, 0.33)	-0.40 (-1.09, 0.29)	-0.34 (-0.94, 0.26)	-0.32 (-0.89, 0.24)	-0.32 (-0.89, 0.25)	1.16 (-1.01, 3.34)
p-value	0.265	0.253	0.259	0.262	0.265	0.284

Multiple linear regression adjusted for age, gender, BMI, waist-hip ratio and socioeconomic status (low, medium, high). Data are presented as mean change (and 95% confidence interval) for one IQR increase in indoor particulate matter concentrations. [¶] – UFP concentrations have been scaled by 10^3.

CHAPTER FIVE – DISCUSSION

This chapter discusses the main findings of this research and where possible, draws comparisons to other relevant studies and published data. The strengths and limitations of the study are also presented along with a discussion of the clinical implications of the study, and how this research translates to relevant outcomes. Future research recommendations are also provided.

To our knowledge, this is the first study to explore associations between quantitatively measured residential indoor air pollutants with such a comprehensive range of sub-clinical CM outcomes in a high-income country. Whilst all pollutants measured were at low level concentrations when compared with relevant Australian and international standards, we detected numerous statistically significant associations between domestic exposure to both PM and gaseous pollutants with various functional intermediate CM risk biomarkers in an apparently healthy, middle-aged population.

Research considering exposure effects between ambient (outdoor) air pollution with various CM outcomes has been quite widely studied (Afsar et al., 2019; G. Bell et al., 2017; Hooper & Kaufman, 2018; Jaganathan et al., 2019; Rao, Montresor-Lopez, Puett, Rajagopalan, & Brook, 2015; Riant et al., 2018; Weinmayr et al., 2015). However, in contrast, limited studies exist that examine the effects of residential IAQ on cardiovascular and metabolic health, particularly in high-income countries (Magalhaes et al., 2018; Krassi Rumchev et al., 2018). This is despite it being well reported that in high-income countries, a greater portion of individual daily time is spent at home (Brasche & Bischof, 2005; Lai et al., 2004; Leech et al., 2002; Newby et al., 2015; Schweizer et al., 2007) and although there are some similarities with outdoor air pollution, the composition and toxicity of indoor air pollution is different due to complex and diverse originating emission sources and post emission processes (Morawska et al., 2017).

5.1 Air quality

Much of the research that has examined the associations between health outcomes and air pollution have predominantly been based on exposure to ambient air pollution (Peter Franklin et al., 2019; Kephart et al., 2020; World Health Organisation, 2005). However, significant sources of personal exposure originate from the indoor environment (P. J. Franklin, 2007) with some studies reporting that exposure to indoor-generated PM can contribute to between 10-30% of the global burden of disease (Morawska et al., 2013). Despite this, limited research has been undertaken to investigate the impact of indoor air pollution on adverse human health effects (Abdullahi et al., 2013; Peter Franklin et al., 2019). Additionally, the majority of those studies published, have been carried out in low- and middle-income countries and have focused on the detrimental impacts of burning biomass or coal for cooking and heating homes (Balmes, 2019; J. Baumgartner et al., 2018; J. Baumgartner et al., 2011; Clark et al., 2019; Peter Franklin et al., 2019; Kephart et al., 2020; S. Rajkumar et al., 2018; Sarah Rajkumar et al., 2019; Young et al., 2019).

In higher income countries, indoor levels of pollutants are generally much lower than in developing countries and this is generally attributed to the use of cleaner fuels for cooking and heating and technology advancements for general household activities. However, indoor air quality in these countries are still reported to present significant human health risks (Abdullahi et al., 2013; World Health Organisation, 2010).

5.1.1 The indoor air environment

In the current study, PM summary data revealed that indoor concentrations across all PM size fractions were lower than corresponding outdoor levels which is inconsistent with outcomes reported by several other authors who have described considerably higher indoor pollutant concentrations when compared with outdoor concentrations in high-income countries (Abdullahi et al., 2013; BeruBe et al., 2004; Brown, 2002; P. J. Franklin, 2007). All mean indoor and outdoor concentrations for PM_{10} and $PM_{2.5}$ were below the Australian NEPM-AAQ and WHO air quality guidelines of 50 ug/m^3 and 25 ug/m^3, respectively although no evidence exists to indicate that there is a concentration threshold below which exposure is considered 'safe' (Barnett, 2014; R. D. Brook et al., 2017; Capon & Wright, 2019; Environment Australia, 2017a; Keywood et al., 2016; M. R. Miller & Newby, 2020; World Health Organisation, 2013).

There are a number of reasons why indoor PM concentrations in this current study may be lower than outdoor PM concentrations.

IAQ and the concentration of pollutants is directly related to the rate of air exchange (or the 'leakiness' of the home), indoor emission sources and rates, the depositional characteristics of the particles, the concentration of particles and pollutants outside, and the ventilation efficiency of a dwelling (Buczynska et al., 2014; F. J. Kelly & Fussell, 2019; Morawska et al., 2013).

The role of ventilation in contributing to indoor pollutant concentrations is twofold. Firstly, indoor generated pollutants are removed from the indoor environment by the infiltrating outdoor air, and secondly, ventilation introduces outdoor pollutants indoors (Hänninen et al., 2004). However, of recent times the need for homes with increased energy efficiency has led to dwellings that are better sealed with extremely low ventilation and infiltration rates (P. J. Franklin, 2007; F. J. Kelly & Fussell, 2019; Yu et al., 2009). These improvements in home ventilation and infiltration have also been facilitated due to Australian building regulation changes that no longer require fixed ventilation in individual rooms (Molloy et al., 2012).

Whilst not measured in the present study, ventilation and air exchange rates are important determinants of indoor concentrations of PM, TVOC, HCHO and CO_2 with low air exchange conditions contributing to elevated indoor concentrations (Molloy et al., 2012; Morawska et al., 2017; Rojas-Bracho et al., 2004; Salthammer et al., 2010; Wolkoff & Nielsen, 2010). In the context of this current study, lower PM concentrations suggests that whilst indoor activities and/or household characteristics may potentially impact on PM concentrations, indoor emission sources are not contributing significantly to pollution levels and/or the removal processes (such as ventilation) are sufficient to keep up the balance with contributions from indoor emission (such as cooking, heating, etc.) sources. Natural airflows allowed by open windows to enable ventilation may also be occurring without PM loss and deliberate sealing of homes for security or to maintain homeostatic thermal conditions (due to the use of mechanical means for heating and cooling) could also contribute in prohibiting entrance of outdoor pollutants to the indoor environment. This principle is supported by P. J. Franklin (2007) and Yu et al. (2009) who indicate that in recent years there has been an increasing trend to use mechanical means to control indoor climate, therefore reducing the need for active ventilation.

Furthermore, decreased ventilation can lead to the accumulation of post formation gas-phase pollutants (such as HCHO and other species of VOC) of indoor origin which may alter indoor

chemistry (Morawska et al., 2017; Wolkoff & Nielsen, 2010) and contribute to poorer IAQ. Additionally compounding the issue is that in more recent years, levels of indoor VOC have been further altered by the invention of lower emitting home products (e.g., paints) and wider use of comprehensive labelling systems to identify low emission products (Asikainen et al., 2016; Joint Research Centre of the European Commission, 2013).

It may be for these reasons that average concentrations of indoor air pollutants in this study are considered low when compared to both Australian and international environmental standards (Table 2.1). However, associations between low level concentration exposure to both PM and gaseous air pollutants; including some VOC (BTEX [benzene, toluene, ethylbenzene, xylene]), NO_2, sulphur dioxide; with adverse cardiometabolic health outcomes is well reported in the literature (Bolden et al., 2015; Crouse et al., 2012; Everson et al., 2019; Franchini & Mannucci, 2012; Weichenthal et al., 2014; B.-Y. Yang, Qian, et al., 2018), although the absence of Australian guidelines for IAQ prevents a conclusive evaluation of these findings.

In this study, peak indoor concentrations have not been reported. In previous studies however, some combustion-related indoor activities such as cooking or the use of unflued gas heaters, have been shown to periodically generate higher concentrations of pollutants that exceed outdoor maximum allowable levels by an order of magnitude (Department of Environment and Heritage, 2004; Morawska et al., 2017).

5.1.2 The relationship between indoor air pollutant concentrations with dwelling characteristics and occupant activities

Whilst measuring changes in pollutant concentrations and characterising sources of pollution during specific activities was beyond the scope of this study, we did observe higher concentrations of some pollutants related to certain housing characteristics or occupant activities (Table 4.3 and Table 4.4).

We observed non-significant higher concentrations of gaseous pollutants including TVOC, CO_2 and HCHO when the dwelling was reported to be aged < 10 years. Although it is difficult to draw direct comparisons, Héroux and collegues in a Canadian study investigating the relationship between housing characteristics and indoor concentrations of selected VOC, observed positive trends between newer dwellings (stratified into years ≤ 1953; 1954 – 1963; 1964 – 1977; ≥ 1978) with several VOC. These authors attributed this result to off-gassing

from new furniture and building materials such as paints, varnishes and wood products (Héroux et al., 2008).

We also observed higher concentrations of all size fractions of PM for homes older than 10 years compared to homes < 10 years. This result has been reported in other research and might be a reflection of the increased state of 'leakiness' often associated with older homes (Molloy et al., 2012).

In our study, higher concentrations of all pollutants (other than HCHO) were seen as the numbers of occupants within the home increased. These increases were significant for TVOC ($p = 0.039$) and CO_2 ($p = < 0.001$) and are similar to the findings of an Australian study where elevated concentrations of CO_2, PM_{10} and NO_2 were observed as the number of household occupants increased (DEWHA, 2010). Urso et al. (2015) provides rationale for increasing concentrations of PM describing that particles become more mobile and will be re-suspended from human movement especially as occupant densities increase. Similarly, human respiration is a significant source of CO_2 which provides plausible explanation for elevations in concentrations as the number of household occupants increases.

In the current study and consistent with DEWHA (2010), elevated concentrations of TVOC, CO_2 and CO were shown when households cooked exclusively with gas appliances compared with electric appliances or combinations such as a gas cooktop and electric oven. In contrast, higher concentrations of all PM size fractions were consistently observed when occupants cooked with combination systems compared to exclusive gas or electric cooking. Although only marginally statistically significant, the greatest effect was seen in UFP ($p = 0.093$) and may reflect the type of cooking being undertaken and the timing of monitoring. In a review by Morawska et al. (2013), it was reported that residential indoor sources of UFP originate from cooking (e.g., grilling, baking, frying, toasting), the use of toasters, gas and electric stoves. Although it was beyond the scope of our study to measure PM and UFP concentrations during specific cooking activities, the timing of the monitoring period (4pm – 10pm) would logically coincide with the cooking of an evening meal and thus contribute to higher numbers of UFP.

Similarly, no relationship was noted between PM and regular use (as opposed to never used) of a kitchen extractor fan although regular use of the extraction system was marginally associated with elevated levels of UFP ($p = 0.080$).

L. Wallace, Wang, Howard-Reed, and Persily (2008) offer reason for these results. Whilst exposure to particles can be substantially reduced by using range hoods ventilated outside, the efficiency of an extraction system is affected by the design and flow rate of the fan and some studies have indicated that poor design and low efficiencies are common (L. Wallace et al., 2008). Given this is the case, it is also conceivable that the fan action of a poorly designed, low efficiency extractor system might in fact mobilize UFP, without extracting them. Additionally, L. Wallace et al. (2008) indicate that in the case of UFP, it is possible that their increased Brownian motion[2] will lower the efficiency of range ventilation presumably resulting in elevated UFP numbers as seen in the present study.

In previous studies, cleaning activities such as sweeping, vacuuming and dusting have been identified as a source of larger sized PM, along with resuspension from human movement and activities (Morawska et al., 2013; Urso et al., 2015). This might reasonably explain the significantly higher PM concentrations (except UFP) observed in this current study when fans were reported as the preferred cooling method (i.e., due to resuspension). Other activities included the self-reported frequency of cleaning which was observed to significantly impact UFP numbers and may reflect the formation of secondary particles through ozone/terpene reactions related to d-limonene (a citrus scent in cleaning products) containing cleaning products (Morawska et al., 2013; Rohr, 2013; Rohr, Weschler, Koutrakis, & Spengler, 2003; Weichenthal, Dufresne, & Infante-Rivard, 2007; Wolkoff & Nielsen, 2017). Cleaning frequency however, was not noted to affect PM concentrations in other size fractions.

Type of heating appeared to have more of an influence on gaseous pollutant concentrations with significantly higher concentrations of TVOC ($p = 0.039$), CO_2 ($p < 0.001$) and NO_2 ($p = 0.054$) observed when gas, electric or oil heating was used exclusively in preference to reverse cycle air conditioning (AC) or a combination of heating involving AC and gas, electric or oil. Similar findings were reported for VOC in a Canadian study investigating air concentrations of selected VOC in a sample of residential homes with various characteristics. In this study, significant elevations of benzene, toluene and styrene were observed where the main heating was reported to be gas system (Héroux et al., 2008).

In two Australian studies (Department of Environment and Heritage, 2004; He et al., 2011), higher NO_2 concentrations were associated with the use of gas heating. A similar outcome was

[2] The erratic random movement of microscopic particles, as a result of continuous bombardment from molecules of the surrounding medium (Encyclopaedia Britannica, 2020).

observed in the current study, however our results achieved only borderline statistical significance ($p = 0.054$).

We also observed an association between CO_2 with the use of gas heating, which is a similar result to an Australian IAQ study of 40 dwellings in Melbourne (Molloy et al., 2012). In this study, Molloy et al. (2012) indicated that combustion related to the use unflued gas appliances (or indeed any type of combustion) is a significant indoor source of CO_2 (Molloy et al., 2012), which might provide plausible explanation for our result.

Carpets, glues and underlay have generally been recognized as a source of VOC (Corsi & Rynes, 2000). However, in the current study the presence of carpets or linoleum floor coverings was associated with lower TVOC when compared to ceramic, stone, concrete or wood floor coverings. This is consistent with the findings of Héroux et al. (2008) and explanation is provided by other studies. Carpets/linoleum, soft furnishings, wood particle board and some ceiling materials are known to release or adsorb VOC (Corsi & Rynes, 2000; Elkilani, Baker, Al-Shammari, & Bouhamra, 2003), thereby essentially acting as a 'sink' with the effect of lowering indoor air concentrations of VOC. These VOC are then available to be released back into the air when indoor air or ambient conditions suit (Wilke, Jann, & Brödner, 2004). Furniture, fixtures and fittings therefore have an important and complex relationship with IAQ, and their presence or absence may partly explain concentrations of VOC measured in indoor air. In the current study, it is important to note that specific consideration of some of these factors (soft furnishings, wood particle board, ceiling materials) was beyond the scope of this study and it is possible that some of the observed associations may have been confounded by unknown and/or unmeasured factors and will require further investigation.

In contrast to the above relationship with VOC, we observed elevated concentrations of NO_2 with ceramic, stone, concrete or timber floors when compared to other types of floor coverings. Although our results achieved only marginal significance ($p = 0.058$), this finding is consistent with He et al. (2011), although no definitive explanation was provided by these authors for this result.

Whilst several Australian exposure studies have partly filled some gaps related to IAQ in typical domestic environments (Cheng et al., 2016; Department of Environment and Heritage, 2004; DEWHA, 2010; Dingle & Franklin, 2002; Goodman et al., 2017; Lawson et al., 2011; Morawska et al., 2003), considerable variability in study design, measurement metrics, instrumentation and averaging periods make it challenging to compare results, or to conduct

comparative exposure analyses. This, along with a lack of specific Australian IAQ guidelines or standards, or a standardized protocol, have been common limitations noted in other studies and reports (Environment Australia, 2017b; Morawska et al., 2017).

5.2 The relationship between exposure to air pollution and sub-clinical markers of cardiometabolic risk

Epidemiological and observational studies have established associations between ambient air pollution with a range of intermediate endpoints underpinning cardiometabolic health (Afsar et al., 2019; R. D. Brook et al., 2011; R. D. Brook et al., 2010; Z. Chen et al., 2016; Cicoira, 2018; Trenton Honda et al., 2017; F. J. Kelly & Fussell, 2015; M. R. Miller & Newby, 2020; Rabito et al., 2020; Renzi et al., 2018; Shamy et al., 2018). Several of these studies have also attempted to identify the components of ambient air pollution considered to be most toxic (e.g., elements, PM) and sources (e.g., traffic, industry) with various markers of cardiometabolic risk (Adar et al., 2018; Yutong Cai et al., 2017; Yuanyuan Cai et al., 2016; Chang et al., 2015; S. Chen, Lin, & Chan, 2011; S.-Y. Chen et al., 2012; Jaganathan et al., 2019; F. J. Kelly & Fussell, 2015; Mehta et al., 2014; Rabito et al., 2020; Rohr & Wyzga, 2012; Weichenthal, 2012).

In contrast, exposure studies involving domestic indoor environments are less well studied with the majority of research typically conducted in low- and middle-income countries and/or in populations with very high exposures such as those experienced during cooking activities using biomass or solid fuel (Kephart et al., 2020; Qu, Yan, Qu, & Ikram, 2015; Rabito et al., 2020; Sarah Rajkumar et al., 2019; Krassi Rumchev et al., 2018; Walker et al., 2020). Additionally, many studies have suffered due to small cohorts (Morawska et al., 2013; Northcross et al., 2015) and simplistic approaches in estimating exposures from other pollution sources such active cigarette smoking, second hand smoke, and ambient air pollution (Burnett et al., 2014; Fedak et al., 2019; Landrigan, Fuller, Acosta, et al., 2018; Pinault et al., 2016; Shanley et al., 2016).

In this current study, associations were demonstrated between direct measurements of IAQ with measures of pre-clinical cardiometabolic risk using directly measured IAQ and clinical data (Tables 4.10 - 4.21).

5.2.1 Blood pressure

BP is variable and a well-established marker of CVD risk (R. D. Brook et al., 2010; Fedak et al., 2019; Walzer et al., 2020) that can be affected by various environmental factors (Choi et al., 2019). Whilst recent epidemiologic studies at community and personal-level have suggested that air pollution can lead to adverse fluctuations in BP (Adar et al., 2018; Auchincloss et al., 2008; Robert D. Brook, Hwashin H. Shin, et al., 2011; Chan et al., 2015; Choi et al., 2019; Dvonch et al., 2009; L. Liu et al., 2009; Krassi Rumchev et al., 2018; D.-H. Tsai et al., 2015), the link between air pollution and arterial BP is not well defined (Auchincloss et al., 2008; J. Baumgartner et al., 2018; R. D. Brook et al., 2009; Choi et al., 2019; Giorgini et al., 2016; Liang et al., 2014) and may in some part reflect the inconsistencies in the reporting of BP (single versus repeated versus ambulatory measures) combined with the diverse range of exposure methodologies.

It is generally agreed however, that central measures are clinically superior to peripheral measures of BP (C. McEniery & Cockcroft, 2007; Suleman et al., 2017), and ambulatory monitoring, when compared to single measures of BP, provides a more precise and reliable BP profile (National Heart Foundation of Australia, 2016).

In this current study using central ABP measurements, an IQR increase in NO_2 concentration was associated with a 2.40 mmHg lower 24-hour (95% CI: -4.74, -0.05) and 2.10 mmHg lower daytime (95% CI: -4.02, -0.17) SBP. Although we also saw reductions in nighttime SBP measurements (-1.44 mmHg; 95% CI: -3.75, 0.87), these were not statistically significant. Marginal relationships were also demonstrated between an IQR increase in NO_2 with lower 24-hour peripheral SBP (-2.32 mmHg; 95% CI: -4.95, 0.30), and 24-hour central DBP (-1.67 mmHg; 95% CI: -3.62, 0.28). No other associations were observed between measures of BP and any other indoor gaseous pollutants (Table 4.10).

Support for our findings comes from several observational studies and a recent meta-analysis by B.-Y. Yang, Qian, et al. (2018). In a small European cohort (n = 20) of healthy volunteers aged 59 – 79 years, Scheers et al. (2018) reported SBP reductions of 0.98 mmHg (95% CI: -2.23, 0.26) and 0.14 mmHg (95% CI: -1.17, 0.88); and a DBP fall of 0.66 mmHg (95% CI: -1.52, 0.19) and 0.28 mmHg (95% CI: -1.00, 0.43) with 10 $\mu g/m^3$ increases in ambient and personal NO_2 exposure, respectively. In the Sister Study (women aged 35 – 76 years; n = 43 629), Chan et al. (2015) did not find an association between ambient NO_2 with SBP, however

a 0.2 mmHg lower DBP (95% CI: -0.4, 0.0; $p = 0.05$) was reported. Chuang et al. (2010) did not observe a relationship between systolic or diastolic BP with ambient NO_2 or CO in the population-based Taiwanese TWSHHH study ($n = 7578$ adults aged 16 – 90 years). This is despite that ambient air pollution concentrations are known to be above recognized maximum guideline annual mean values set by the WHO (Argacha et al., 2018; Lim & Thurston, 2019; Riant et al., 2018; World Health Organisation, 2005). Interestingly, Chuang and colleagues (2011) described contrasting results in subsequent work. These authors reported elevations in the magnitude of 14.40 mmHg (95% CI: 10.98, 17.82) and 12.43 mmHg (95% CI: 10.63, 14.23) per IQR increase in NO_2 with SBP and DBP, respectively. However, consistent with the current study, no relationship was demonstrated between BP with exposure to CO.

Although we were unable to establish a significant relationship between any size fraction of PM with BP, we did see consistent rises in SBP (24-hour peripheral, 24-hour central and central daytime), and falls in DBP (24-hour peripheral, 24-hour central, central daytime and central nighttime) per IQR increase in TPM, PM_{10}, PM_4, $PM_{2.5}$ and PM_1 (Table 4.11).

These findings are consistent with several other ambient air exposure studies. Dvonch et al. (2009) and D.-H. Tsai et al. (2015) both observed rises in SBP with increases of 10 $\mu g/m^3$ in $PM_{2.5}$ and PM_{10}, respectively. No relationship was shown with DBP. In the NHANES III, an IQR increase in PM_{10} was associated with higher SBP and lower DBP in fully adjusted models (Shanley et al., 2016). Both the MESA-Air (Auchincloss et al., 2008) and Sister Studies (Chan et al., 2015) also observed higher SBP with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and no relationship with DBP. In a very recent study conducted in Korea by Choi et al. (2019), no relationship was shown between short-term exposure to ambient PM with BP. In a further study conducted in Taiwan, where ambient air pollution levels are known to be considerably higher than in Europe or North America (Argacha et al., 2018; Lim & Thurston, 2019; Riant et al., 2018; World Health Organisation, 2005), small elevations in SBP were observed with increases in 1-day averaged PM_{10}, however no relationship was shown with DBP (Chuang et al., 2010).

Potential explanations for our results are provided in the literature. Firstly, levels of pollutants may have been too low to elicit a significant response and might require a longer cumulative duration of exposure in order to produce a significant effect on cardiovascular ill health and/or vascular dysfunction (Giorgini et al., 2016; Willocks et al., 2012). Additionally, it might also be that the pollutant constituents in the 'mix' might have contributed to the lack of response. In a study by R. D. Brook et al. (2009), a combination of ambient $PM_{2.5}$ and ozone exposure

caused arterial vasoconstriction. In further work, Brook and colleagues (2009) assessed the systemic response to a similar multipollutant exposure and demonstrated an elevation in diastolic and mean arterial BP which was associated with PM, but not with ozone concentration (R. D. Brook et al., 2009; Urch et al., 2005). In a more recent review, cardiovascular effects including alterations to heart rate and heart rate variability were reported dependent on individual perception of pleasantness/unpleasantness of certain fragrances related to reaction mixtures of specific VOC and ozone (Wolkoff & Nielsen, 2017). These findings are consistent with the hypothesis that sub-optimal changes in BP might be dependent in some part on the individual constituents in the pollutant mix however, further research is required to elucidate the components in the mix that contribute, and their relative contribution to sub-optimal BP outcomes.

It is also known that a close temporal relationship exists between air pollution exposure and CV outcome (Langrish et al., 2012). In a controlled human exposure study investigating acute responses in BP following exposure to $PM_{2.5}$ emissions from cookstoves, Fedak et al. (2019) observed small decreases in SBP immediately after exposure, and a larger delayed increase in SBP, 24-hours after exposure. Further evidence is provided by Dvonch et al. (2009) in a community-level study which demonstrated significant associations between increases in SBP and daily elevations in $PM_{2.5}$ in 347 adults living in Detroit, Michigan. Much larger effects were observed 2 – 5 days after exposure to higher $PM_{2.5}$ levels.

In the context of the current study, it is possible that elevations in BP may have occurred that coincide with peak concentrations of pollutants achieved during particular domestic events (e.g., cooking, cleaning). Although it was beyond the scope of the study to link temporality of exposure (i.e., the timing of higher concentrations of pollutants) with outcome, given that different pollutants have been shown capable of eliciting different responses (R. D. Brook et al., 2009; Choi et al., 2019; Urch et al., 2005), it is reasonable to assume that these different effects could be achieved with varying time lags dependent on the pollutant. These timing differences in pollutant induced effects was observed in a Korean study where no significant associations were observed between SBP with exposure to ambient $PM_{2.5}$ and PM_{10} from 0 - 8 hours before BP measurements. Gaseous pollutants however, showed significant lag effects with CO significantly reducing SBP at 3 - 5 lag hours and NO_2 significantly elevating SBP at 0 - 2 hours (Choi et al., 2019).

It is also possible that the complex assortment of gaseous and particle pollutants contributing to the indoor mix might result in competing vasoconstricting and vasodilatory effects that manifest differently across diverse pollutant combinations. For example, co-emitted concentrations of TVOC may have elicited a vasodilation response that clouded an acute PM mediated BP elevation. We do not however have sufficient data to further support this theory and further research is deserved to explore this hypothesis.

Prior controlled human exposure studies with diesel particles and concentrated $PM_{2.5}$ have shown that rises in BP occur immediately upon short-duration exposures, but do not stay elevated after particle inhalation stops (subsiding within a few minutes to hours) (D. R. Brook et al., 2002; R. D. Brook et al., 2017; R. D. Brook et al., 2009; E. K. Cosselman et al., 2012; Fedak et al., 2019; Urch et al., 2005). Although it is also possible that increases in BP attributable to intermittently higher concentrations of individual pollutants may have been missed, in a study such as this where there is little control over the types and concentrations of pollutants emitted in each household and the subsequent timing of a response, it would be difficult to nominate the specific exposure responsible for an outcome. It is important to note however, that whilst some work has been undertaken to better understand the exposure-response relationship for some pollutants (R. D. Brook, 2017; E. K. Cosselman et al., 2012; Shaowei Wu et al., 2013), future studies are required that can assist with clarifying this issue, and which assess BP responses concurrently with exposure.

Finally, although the larger literature appears to generally support associations between air pollution and BP (Adar et al., 2018), inconsistencies across studies suggest that the evidence remains unconvincing.

5.2.2 Central hemodynamic indices and arterial stiffness

In the current study, significant associations were established between some pollutants and measures of arterial stiffness (AIx, AIx_{75}, PP, PWV). No relationship however, was observed between any pollutant and more steady components of BP including central MAP or AP (Tables 4.12, 4.13, 4.14 and 4.15). Whilst studies investigating exposure to air pollutants with hemodynamic indices such as MAP and AP are limited, our findings are consistent with those of Auchincloss and colleagues (2008) in the MESA-Air who reported no effect on MAP using 30-day mean $PM_{2.5}$ exposure. Similarly, in the US Sister Study (women aged 35 - 76 years; n = 43 629), no difference was shown in MAP with exposure to NO_2, however a small but

significant rise in MAP (0.8 mmHg; 95% CI: 0.2, 1.4; $p = 0.01$) was demonstrated with 10 $\mu g/m^3$ increases in $PM_{2.5}$ (Chan et al., 2015).

Arterial stiffness, recognized as an established marker of vascular aging, provides information on the risk of future CV events beyond that of established measures such as peripheral BP (Vlachopoulos et al., 2010; Vlachopoulos et al., 2005; Walker et al., 2020). Measures of arterial stiffness such as AIx, PP and PWV, are indicators of overall CV performance with higher values representing increased risk for adverse CV outcomes (Vlachopoulos et al., 2010; Walker et al., 2020).

Studies of ambient air have provided varying evidence that exposure to particulate and gaseous components of air pollution is associated with impaired arterial stiffness (Adamopoulos et al., 2010; Lenters et al., 2010; Mehta et al., 2014). However, separately from the present study, only one other study could be located that has investigated the association between these outcomes with residential air pollution exposure. In a study population of 205 rural Chinese women (aged 27 - 86 years) exposed to elevated levels of fine PM ($PM_{2.5}$) related to biomass cooking, Baumgartner and colleagues reported higher central BP, PP and AIx (J. Baumgartner et al., 2018).

In the current study, the greatest and most consistent significant effects were observed between TVOC and HCHO with AIx and AIx_{75} (Table 4.12). Although no previous studies could be found that reported on the relationship between TVOC and HCHO with any measure of arterial stiffness, potential explanations for our findings is provided by the literature.

Increased arterial stiffness associated with vascular damage can be either structural or functional in nature although traditional CVD risk factors such as hypertension, and dyslipidemia contribute to both structural and functional vascular damage (Tomiyama & Yamashina, 2010; Zanoli et al., 2017). Arterial stiffness is the principle cause of CVD with age (O'Rourke & Hashimoto, 2007; Tomiyama & Yamashina, 2010) and advancing age is associated with hypertension and the risk of CV events (Kaess et al., 2012; Ljungman et al., 2018). These outcomes are better described by a process of underlying *structural* change (O'Rourke & Hashimoto, 2007; Tomiyama & Yamashina, 2010).

Increased inflammatory markers as might be seen in inflammatory conditions such as rheumatoid arthritis, have been linked to adverse vascular changes including hypertension and increased central arterial stiffness (G. T. Kim et al., 2014; Ljungman et al., 2018; Muhammad

et al., 2017; Petra et al., 2019; Turesson et al., 2005) causing *functional* stiffening of the arteries (Tomiyama & Yamashina, 2010). However, as would be reasonably expected in this type of circumstance, a reduction in inflammation has also been shown to lead to reductions in central arterial stiffness (Ljungman et al., 2018; Mäki-Petäjä et al., 2012; C. McEniery & Cockcroft, 2007).

Because pollution is linked to adverse alterations of blood biomarker levels that stimulate inflammation and endothelial dysfunction (D. R. Brook et al., 2002; Ljungman et al., 2018; Peters et al., 2001; Urch et al., 2005) [these conditions are both associated with functional arterial stiffening (C. McEniery & Cockcroft, 2007; Zanoli et al., 2017)], it is conceivable that inflammation might be responsible for the stiffening of large arteries after exposure to air pollution even at acute, low-level and transitory exposure and might be related to a functional arterial stiffening response (Zanoli et al., 2017). Additionally, evidence also exists to suggest that exposure to air pollution is associated with acute arterial vasoconstriction (D. R. Brook et al., 2002) which may lead us to conclude that increases in augmentation index seen in our healthy population, could be the result of air pollution-mediated vasoconstriction at microcirculation level. This can result in the early arrival of the return of pulse wave reflection from the periphery (O'Rourke & Hashimoto, 2007) (Figure 2.7) reflecting functional rather than structural changes in arterial stiffness. This position gathers some support from Adamopoulos et al. (2010) and Zanoli et al. (2017) and furthermore, by Lenters and colleagues who in the Atherosclerosis Risk in Young Adults study, examined the relationship between ambient NO_2, $PM_{2.5}$, black smoke and sulphur dioxide with indicators of vascular damage and concluded that even low levels of air pollution exposure may cause early vascular damage (Lenters et al., 2010).

A further explanation is provided by P. R. Kelly, Millasseau, Ritter, and Chowienczyk (2001) and Walker et al. (2020) who indicate that alterations in PWV and AIx can occur independently, depending on which section of the arterial tree is most influenced by the exposure. The mechanisms of stiffening differ according to the region of the arterial tree because the properties of the arterial wall vary along the longitudinal axis of the arterial tree (e.g., elastic arteries are dominated by elastic fibres and muscular arteries are dominated by collagen and smooth muscle cells) (O'Rourke & Hashimoto, 2007; Tomiyama & Yamashina, 2010).

That said and in the context of the present study, it is conceivable that short-term recent exposures to all or selected VOC might have altered endothelial function in conduit and elastic arteries, with the intermediate but potentially transient effect of increasing arterial stiffness. However, this hypothesis requires further, more focused investigations to clarify the relationship and whether, if this theory is correct, reduction of exposure to these pollutants is associated with a reduction of arterial stiffness.

In the current study, an inverse relationship was observed between higher levels of NO_2 with 24-hour and nighttime PP. This same inverse relationship was also demonstrated with daytime PP, although only achieved marginal significance (p = 0.053) (Table 4.13). Whilst this relationship is a surprising finding, other studies including the large Framingham Heart Study Offspring and the Third Generation cohorts (n = 5842) (Ljungman et al., 2018), have reported similar results to those seen in this current study. Scheers et al. (2018) also demonstrated a 10 $\mu g/m^3$ increase in personal NO_2 resulted in lower PP, and Chen and colleagues (2012) reported reductions in PP with exposure to ambient NO_2 and a range of other pollutants including PM_{10}, SO_2, CO and ozone (S.-Y. Chen et al., 2012).

UFP were the only particle size to demonstrate an association or a marginal relationship with measures of arterial stiffness (Table 4.14 and Table 4.15). Associations were observed with all indices of arterial stiffness measured in this study (AIx, AIx_{75}, PP, PWV), over all time frames (24-hours, daytime, nighttime), although this relationship was consistently inversed with PP (other than nighttime which did not show a relationship) and PWV.

Whilst studies of associations between UFP exposure and sub-clinical measures of arterial stiffness are limited, Ljungman et al. (2018) was not able to establish an association between higher concentrations of short-term exposure to ambient UFP, with multiple measures of arterial stiffness in the Framingham Heart Study cohort. This was despite UFP numbers being significantly higher (range: 3791 – 63 866 particles/cm^3) when compared to the current study (range: 975 – 35 941 particles/cm^3).

These results are also consistent with the findings of Soppa et al. (2019) who in a randomised sham-controlled study noted rapid increases in AIx and no effect on PWV in a German population, with exposure to fine and UFP originating from typical indoor sources. Whilst this outcome is aligned with recent evidence for ambient UFP which shows that UFP exposure can have an appreciable impact on the CV system (Ohlwein, Kappeler, Kutlar Joss, Künzli, & Hoffmann, 2019; Soppa et al., 2019), in a recent review of literature, Ohlwein et al. (2019)

noted that in real-world and controlled human exposure studies to UFP, altered endothelial function and increased markers of inflammation were observed, although these authors concluded that much work remains to confirm these relationships.

While associations were observed between a number of pollutants with AIx, no significant relationships were shown between PWV with any pollutant. Other studies have produced similar results providing support for the findings of the present study (J. Baumgartner et al., 2018; Lenters et al., 2010; Scheers et al., 2018; C.-F. Wu et al., 2016)

This lack of a significant association however is not evidence for no association, with Walker et al. (2020) suggesting it may be a reflection of the complex nature of the mix of pollutants. Results from the current study did not provide any clear evidence to suggest that a specific pollutant was associated with changes to PWV. However, it is possible that the compound nature of pollutants emitted into the home environments of the study population, resulted in mixtures of pollution that impacted health outcomes to a similar degree. Furthermore, the range of exposures experienced during the 24-hour monitoring period potentially may not have been large enough to discern detectable differences in the magnitude of the changes in PWV. Multipollutant characterization of a wider range, and sources of pollutant in future research may help to provide a better understanding of these remaining uncertainties.

Regarding the mechanism involved, inhalation of particulate and gaseous pollutants has been associated with important alterations to vascular tone, endothelial function, the autonomic nervous system and systemic inflammation (Robert D. Brook, Alan B. Weder, et al., 2011; Lenters et al., 2010; Mehta et al., 2014; Urch et al., 2005) and these factors may potentially interact with the arterial wave reflections (Adamopoulos et al., 2010). Regardless of pathophysiological mechanisms however, the heightened magnitude of the reflection wave pressure arriving to the aorta, results in important hemodynamic alterations that adversely affect cardiovascular function. And importantly, our findings add general support to the small body of evidence that low-concentration exposure to some air pollutants may adversely impact central hemodynamic measures and/or arterial stiffness. However, further studies are required to elucidate which of the many pollutants and associated pollutants in indoor residential air, may be responsible for the adverse impacts on vascular function observed in this study.

5.2.3 Lipid, glucose and renal biomarkers

5.2.3.1 Blood lipid profile

Dyslipidemia is widely considered as a modifiable and key risk factor for CVD (Mao et al., 2020; Rutter, Meigs, Sullivan, D'Agostino, & Wilson, 2005) and refers to a lipid pattern of higher TC, TG and LDL levels, and lower levels of HDL (Mao et al., 2020; X.-Y. Zhang et al., 2020).

Although previous research has shown air pollution is capable of promoting dyslipidemia (D. G. Bell et al., 2017; H. H. Chen et al., 2020; Z. Chen et al., 2016; Chuang et al., 2011), studies are limited (Chuang et al., 2010; Chuang et al., 2011) and have mostly evaluated ambient exposures to PM and/or very limited gaseous pollutants (usually NO_2). Additionally, these studies have generally been undertaken in low- and middle-income populations (D. G. Bell et al., 2017; Chuang et al., 2010; Mao et al., 2020; McGuinn et al., 2019; B.-Y. Yang, Bloom, et al., 2018; Yitshak Sade et al., 2016), or in household environments where cooking is undertaken using biomass or solid fuels (Sarah Rajkumar et al., 2019) and pollutant exposure concentrations are far greater than those observed in the present study.

In the current study, gaseous pollutants appeared to have a greater effect on blood lipids than PM (Table 4.16 and Table 4.19). CO_2 was significantly associated with lower HDL levels and higher TC/HDL ratios although unexpectedly, was inversely associated with TC. Several borderline associations were demonstrated between higher TVOC levels with lower HDL and a higher TC/HDL ratio, and unexpectedly, between higher NO_2 concentrations with lower TC. No relationships were observed between any of the gaseous pollutants with LDL and TG, or between PM and any lipid biomarker. This lack of association between PM and any lipid biomarker is however supported by several other studies where plasma lipid levels have not been affected by PM (frequently PM10 and/or PM2.5) air pollution, over various windows of exposure (D. G. Bell et al., 2017; Z. Chen et al., 2016; Chuang et al., 2011; Sarah Rajkumar et al., 2019; Xiao et al., 2016).

Although a relationship was not established, TG levels were observed to consistently lower with increasing exposure to all size fractions of PM. Although this outcome was unexpected, these findings have also been seen in a number of very recent studies involving a variety of study populations. Mao et al. (2020) and Sarah Rajkumar et al. (2019) reported a lowering of

TG levels in a Chinese rural population exposed to high-level air pollution and in 150 Honduran woman cooking with biomass, respectively. The same outcome was described in a study of early life PM exposure in Mexican children (McGuinn et al., 2020).

Despite observing limited relationships between pollutants and lipid levels in the current research, explanations for these outcomes are provided in the literature.

Similar to BP, our findings may have been subject to differing lag effects for individual blood lipid markers. In a study by Xiao et al. (2016), the relationship between blood lipid markers in hypertensive patients complicated with or without T2DM was explored to ascertain whether they were affected by exposure to air pollution. Although our study population profile was somewhat different to the study population of Xiao and colleagues, these authors demonstrated that there was no consistent certainty for the required exposure time to elicit a response for a particular blood lipid marker, and the effects of air pollution on one blood lipid marker did not necessarily correspond with other lipid markers. However, a trend was identified in that prolonged exposure time to air pollution was accompanied by more significant changes in blood lipid levels, perhaps indicating a potential cumulative exposure effect. This effect has also been observed in other studies (D. G. Bell et al., 2017; Xiao et al., 2016). Further research is required to clarify this relationship, particularly to determine whether the same trend is observed in healthy populations.

Additionally, and similar to Xiao and colleagues (2016), we only measured levels of blood lipid markers however the function may also be affected. Further research is also required to evaluate this.

5.2.3.2 Glucose metabolism

Ambient air pollution exposure studies have demonstrated links with broad metabolic derangements in glucose and insulin homeostasis (including glucose intolerance, decreased insulin sensitivity, and impaired secretion) (Benjamin Bowe et al., 2018). However, domestic air pollution exposure studies are limited (Lim & Thurston, 2019; Riant et al., 2018) and mostly the work has emerged from low- and middle-income countries (S. Rajkumar et al., 2018; Sarah Rajkumar et al., 2019) where household cooking and heating relies on solid fuels, and domestic exposure is likely to be very different to the current study.

In this present study, whilst no association was established between any size fraction of PM with fasting glucose, we did observe small decreases in fasting glucose with higher levels of PM (Table 4.20). This finding gathers support from the US Meta-AIR study, which also observed drops in blood glucose levels with short-term exposure to PM_{10} and $PM_{2.5}$ (J. S. Kim et al., 2019), and also in a study conducted in 28 peri-urban villages in Southern India where individuals were exposed to high-levels of indoor and outdoor $PM_{2.5}$ (Curto et al., 2019). In comparison, Yitshak Sade et al. (2016) reported similar but mixed results, which is a consistently stated limitation of research investigating the relationship between air pollution exposure and measures of glucose homeostasis (L. Chen et al., 2016; Trenton Honda et al., 2017; Li et al., 2018; Cong Liu et al., 2016; S. A. Lucht et al., 2018; Rajagopalan & Brook, 2012; Wolf et al., 2016). Using 3-month averaged data, Yitshak Sade et al. (2016) reported a rise in fasting glucose per IQR increase in PM_{10} however observed a fall in fasting glucose per IQR exposure to $PM_{2.5}$.

Limited studies have explored the relationship between gaseous pollutants and fasting glucose, although similar to this research, J. S. Kim et al. (2019), S. A. Lucht et al. (2018) and Riant et al. (2018) also did not observe a relationship between fasting glucose with ambient NO_2 at low-concentration (below WHO threshold) levels (annual mean of 40 $\mu g/m^3$). In contrast, in a high-concentration exposure study conducted in Taiwan using 1-year averaged data for ambient air pollutants, NO_2 was found to be associated with higher fasting glucose (Chuang et al., 2011).

Similar to studies investigating air pollution mediated effects on fasting blood glucose, a paucity of studies exists that investigate the relationship between air pollution exposure and longer-term glycaemia measures such as HbA1c (Trenton Honda et al., 2017).

Although positive associations have been shown between the effects of (ambient) PM exposure with HbA1c (Chuang et al., 2010; Cong Liu et al., 2016; S. A. Lucht et al., 2018; Riant et al., 2018), this contrasts to the findings of the present study which failed to establish a relationship between any PM size fraction with HbA1c (Table 4.20). Similar results to ours however, have been demonstrated in other research (Yutong Cai et al., 2017; Trenton Honda et al., 2017; Kephart et al., 2020; Li et al., 2018).

No relationship was established between any of the gaseous pollutants measured in the study with HbA1c other than CO_2 where a small but significant (0.08%; 95% CI: 0.00, 0.17; p = 0.041) rise in HbA1c was observed per IQR increase in CO_2 (Table 4.17). Although NO_2 exposure was not associated with HbA1c, this result is similar to the findings of Yutong Cai et

al. (2017). In contrast, Honda and colleagues (2017) reported a significantly higher HbA1c per IQR increase in NO_2 and suggested that NO_2 (a surrogate measure for traffic related pollution), might be an important predictor of HbA1c.

Given the paucity of evidence for the relationship between residential air pollution exposure with measures of glucose homeostasis, and the inconsistencies between study findings exploring the relationship with ambient air, further research is required to clarify and understand both the long- and short-term effects of domestic indoor air pollution exposure with unfavourable effects on measures of glucose metabolism.

5.2.3.3 Renal function

The kidneys are high-flow, low impedance organs that are highly susceptible to pulsatile damage (Mitchell, 2008; Townsend et al., 2015) that may be exacerbated by exposure to particulate matter and gaseous air pollutants. Almost 20% of cardiac output is supplied to the kidneys, where the blood is filtered and environmental pollutants can be concentrated (Afsar et al., 2019; Wang et al., 2020; Xin et al., 2018). Although diabetes and high BP are major causes of chronic kidney disease (CKD) in most middle- and high-income countries, recent evidence suggests that exposure to environmental pollutants such as PM and heavy metals, might also be a novel risk factor for end-organ damage including CKD (S.-Y. Chen et al., 2018; H.-J. Kim et al., 2018; Mehta et al., 2016; Xin et al., 2018; Y.-R. Yang et al., 2017) and may be the consequence of microvascular alterations and compromised regulation of local blood flow associated with increased arterial stiffness.

Previous epidemiological studies have reported significant associations between exposure to ambient air pollution with various measures of renal function (Lue et al., 2013; Mehta et al., 2016; Y.-R. Yang et al., 2017). However, no studies were found that investigate the relationship between residential air pollution exposures with sub-clinical measures of renal function. Current evidence relies on ambient air pollution exposure studies that use a range of renal function indicators when reporting outcomes which have yielded mixed results (Afsar et al., 2019; Bowe et al., 2017; Bowe et al., 2020; H.-J. Kim et al., 2018; B. Liu, Fan, & Huang, 2020; Lue et al., 2013; Mehta et al., 2016; M. S. O'Neill et al., 2008; Wang et al., 2020; Xin et al., 2018).

In the current study, although no relationship was established between conventional size fractions of PM (TPM, PM_{10}, PM_4, $PM_{2.5}$, PM_1) with any marker of renal function, we did

unexpectedly observe borderline inverse associations between ACR with UFP (-0.38 mg/mmol; 95% CI: -0.79, 0.04; $p = 0.071$) and CO_2 (-0.22 mg/mmol; 95% CI: -0.47, 0.03; $p = 0.087$) (Table 4.21).

One possible explanation for this result may be related to the measurement of albumin and creatinine levels to ascertain the ACR. A single voided urine sample was used to measure ACR rather than repeated measurements or a timed collection. Considerable intraindividual daily variations in albuminuria (Mosenzon et al., 2015) and a single urine sample may not be as accurate as measuring a 24-hour albumin excretion or first voiding urine. This is a limitation reported in other studies (Chin et al., 2018).

Interestingly however, in a recent study investigating the prognostic value of urinary albumin excretion for cardiovascular risk assessment, Scirica et al. (2018) indicated it was not known whether ACR is a causal or spectator marker of cardiovascular risk such that lower ACR as such would result in improved outcomes. Further studies are required to clarify the role and nature of ACR as a cardiovascular risk marker.

None of the pollutants measured in this present study were associated with urinary albumin excretion other than a marginal relationship with exposure to HCHO (1.39 mg/L; 95% CI: -0.17, 2.95; $p = 0.080$) (Table 4.18).

Only one other study could be identified that measured urinary albumin excretion as a renal function indicator and found that chronic and recent PM_{10} exposure was not associated with ACR or microalbuminuria. Additionally only weak evidence was found to support that the progression of albuminuria was accelerated among those with chronic exposure to PM_{10} (M. S. O'Neill et al., 2008).

5.3 Comparisons with other studies and interpretations

Whilst there is a body of literature that has reported on a range of air pollution-induced adverse cardiometabolic effects including vascular changes leading to sub-optimal BP (R. D. Brook, 2017; Choi et al., 2019; Kephart et al., 2020; Young et al., 2019), increased arterial stiffness (Lenters et al., 2010; Ljungman et al., 2018; Mehta et al., 2014; Walker et al., 2020; Zanoli et al., 2017), metabolic derangements such as impaired insulin sensitivity (S. A. Lucht et al., 2018; S. Rajkumar et al., 2018; Riant et al., 2018; Yitshak Sade et al., 2016) and unfavourable

changes to renal function (Afsar et al., 2019; Bowe et al., 2020; B. Liu et al., 2020; Wang et al., 2020; Xin et al., 2018), the evidence available is generally inconsistent.

The specific reasons for these inconsistencies between studies of air pollution exposure and associated health outcomes is not clear, however might partly be explained by differences in study methodology including study design and sample size, regional characteristics, population characteristics, constituents of air pollution mixtures, lag periods, averaging times for exposure and the selection of monitoring instrumentation (Choi et al., 2019; B. Liu et al., 2020; Ljungman et al., 2018; Ohlwein et al., 2019; B.-Y. Yang, Qian, et al., 2018).

Similar variability has been described in the measurement of cardiometabolic risk factors including methods for determining BP (single versus repeated versus ambulatory measures) (Auchincloss et al., 2008; R. D. Brook et al., 2011; Dvonch et al., 2009; D. H. Tsai et al., 2012), vascular function (Ljungman et al., 2018) and reporting metrics of glucose metabolism and renal function.

5.3.1 Methodological limitations of previous research

Some of the major obstacles in reaching considered conclusions on the differential toxicities of both PM and gaseous pollutants are the limitations in the methodologies of experimental research.

Previous studies have reported on relationships between indoor and outdoor air pollution and health using exposure metrics where the individual was not directly observed (Wilson et al., 2005). In these studies, estimations of exposure have been made by extrapolating an exposure value or exposure variation from one or several fixed site locations, applied to the entire population of the study area (Adamopoulos et al., 2010; Bourdrel et al., 2017; Chang et al., 2015; S.-Y. Chen et al., 2012; Elvidge, Matthews, Gregory, & Hoogendoorn, 2013; T. Honda et al., 2018; F. J. Kelly & Fussell, 2012; S. Liu et al., 2017; McGuinn et al., 2019; Mudway et al., 2020). However, this approach may lead to exposure misclassification and potentially biased health risk results as characteristics of individual exposure may be wrongly inferred from characteristics of the collective population (Bourdrel et al., 2017; Wilson et al., 2005).

Similar limitations have been reported when contemplating individual level sub-clinical cardiometabolic health effects. Studies have frequently reported on clinical outcomes including stroke, coronary heart disease, MI along with prevalence and incidence of T2DM, with

information ordinarily derived through institutional health data, or by self-report (Barnett et al., 2006; Bourdrel et al., 2017; R. D. Brook, Cakmak, et al., 2013; I. Eze et al., 2014; Milojevic et al., 2014; Pinault et al., 2016; C. A. Pope, 3rd et al., 2015; Stafoggia et al., 2013; Antonella Zanobetti & Schwartz, 2005). Individually assigned health data generated from these sources is then typically linked to the extrapolated exposure data to determine the directionality of a relationship. In turn, this potentially leads to incorrect classifications due to wrongly concluded assumptions about an individual's health status and/or the nature and concentration of individual level pollutant characteristics (Mudway et al., 2020; Wilson et al., 2005).

Although infrequently acknowledged, these various disparities and lack of standardisation in experimental conditions are common limitations reported in published literature (Bourdrel et al., 2017; Fisk et al., 2018; Gilbey et al., 2019; Goodman et al., 2017; F. J. Kelly & Fussell, 2012; B. Liu et al., 2020; M. R. Miller & Newby, 2020; Mudway et al., 2020; B.-Y. Yang, Qian, et al., 2018) and hamper comparability of reported findings between studies. Despite this however, comparisons are frequently made among studies (Goodman et al., 2017).

5.4 Strengths, limitations and recommendations for future research

This study has several notable strengths above the contribution it adds to the increasing body of evidence related to the impact of residential air pollution exposure on sub-clinical indicators of cardiometabolic risk.

Firstly, and importantly, this study benefitted from a relatively homogenous random sample of apparently healthy, well-characterised, middle-aged adults living in a geographical area where outdoor air pollutant (contributing to total exposure) concentrations are fairly consistent, and typically below accepted air quality standards. Additionally, all environmental and clinical data were directly measured without relying on surrogates or self-report. Potentially this reduces the opportunity for introduced bias related to exposure and outcome misclassification commonly reported as a limitation in other studies (Curto et al., 2019; Li et al., 2018)

Another important strength of this study was the high temporal resolution permitted by 24-hour ABPM. This also allowed for the examination of different time frames (24-hours, daytime, nighttime) and provided a more reliable individual BP profile whilst also incorporating the normally occurring daily fluctuations in BP.

Additionally, this research relied on central ABP measures. Emerging data supports the superiority of ambulatory monitoring in comparison with repeated or one-off clinic-based measurements (Wilkinson et al., 2014). This concept is supported by Vlachopoulos and colleagues in a systematic review and meta-analysis which explored the predictive value of central pressures and the use of associated central hemodynamic indices for CV outcomes. These authors concluded that central pressures and indices confer a significant prognostic value in CV risk prediction (Vlachopoulos et al., 2010).

However, this study is not without its limitations.

The cross-sectional, exploratory nature of the study limits the establishment of a temporal relationship and provides no indication of the sequence of events. The observed impacts on biomarkers at one time point may have occurred before the onset of adverse health effects due to air pollution exposure. It is therefore not possible to evaluate the potential for causality in any of the reported associations.

Furthermore, IAQ was measured on one occasion for a 24-hour period. This snapshot of IAQ concentrations, combined with the temporal mismatch between exposure to indoor air pollutants and the clinical assessment (excluding ABPM) requires us to assume that IAQ concentrations measured during the in-home assessment meaningfully represent long-term concentration configurations within a household, and that the clinical data obtained during the clinic-based assessment similarly represents a long-term cardiometabolic outcome status. Similarly, as most cardiometabolic biomarkers were assessed at a single visit for each participant, we were not able to analyse air pollution exposure in relation to a longitudinal change in pre-clinical cardiometabolic parameters. More detailed longitudinal studies and experimental designs are needed to determine exposure-response relationships between specific air pollutants with adverse cardiometabolic outcomes. This could also be combined with studies that assess the impact of interventions that decrease air pollution (Afsar et al., 2019).

A further limitation is the difficulty in understanding the timing of the onset of an effect and whether an association represents an acute reaction to the current state of pollutant exposure or the result of a lag effect. This should be confirmed in longitudinal analysis utilising a repeated measures study design which may help to map the onset of adverse effects with exposure to specific indoor air pollutants.

This current study assessed in-home exposures and not personal exposures. Although it has been observed in other studies that individuals spend a relevant part of their daily time in their home (Brasche & Bischof, 2005; Lai et al., 2004; Leech et al., 2002; Newby et al., 2015; Schweizer et al., 2007), it is difficult to conclude whether time-activity patterns in this study would affect our findings (e.g., within home versus away from home exposure, home versus occupational exposure).

Additionally, some known CMD risk factors and potential confounding factors such as physical activity and dietary intake were not addressed in this study. Given the study population was selected for its inherently healthy profile and self-reported or measured known confounding factors are within acceptable limits (e.g., BMI, medication and alcohol intake), it is considered that additional residual confounders would also likely fall within tolerated ranges. Reported use of alcohol and medications was low and bivariate analyses confirmed no meaningful associations between these variables and any of the pollutants. Despite this, whilst most important variables were included in the adjusted models, unknown and residual confounding cannot be completely eliminated as explanation for the observed associations. Similarly, observed inverse and/or adverse relationships may also be the consequence of unmeasured or incomplete data on relevant confounders, instrument and methodological errors or measurement error of personal behaviours influencing exposure (e.g., alcohol intake, types of medications used), thus potentially introducing bias in the reporting of unfavourable health effects. This is a common limitation consistently reported in similar recent studies (Bowe et al., 2020; Curto et al., 2019; Kephart et al., 2020). Further analyses of these relationships utilising different study designs and addressing additional identified confounders, including inter-relationships between pollutants, are recommended to corroborate the findings of this current study.

It is also important to acknowledge that both indoor and outdoor air pollution is a complex combination of PM and gases that rarely occur in isolation to each other or other environmental exposures (e.g., temperature, noise) (Argacha et al., 2018; R. D. Brook, 2017; Robert D. Brook, Alan B. Weder, et al., 2011; Claeys et al., 2017; T. Munzel et al., 2017a; T. Munzel et al., 2017b; Xin et al., 2018). Whilst this study has investigated specific and single pollutant associations, it is known that pollutants such as volatile components, can associate or interact with gaseous and particulate phases of air pollution (F. J. Kelly & Fussell, 2012; M. R. Miller & Newby, 2020) creating ‘mixtures’ of pollutants that lead to additive or synergistic health effects. The total harmful effect prompted by combinations of pollutants including different

size fractions of PM combined with gases (NO_2, CO_2, CO), has only more recently received scientific interest (Yuanyuan Cai et al., 2016; Mustafić et al., 2012; Shah et al., 2015; Song et al., 2016), although research exploring the effects of co-exposure to multiple indoor air pollutants is limited. However, it is conceivable that the adverse health effects observed in this current study which have been attributed to single PM and gaseous air pollutants, are the resulting impact of the underlying toxicity of the complete mixture of all air pollutants. In contrast, TVOC are a combined 'mix' of various sub-species and classes of volatile components. Studies have demonstrated a range of adverse health effects related to individually characterised VOC (Cakmak et al., 2014; Ralph J. Delfino et al., 2010) and it is possible that the observed cardiovascular-related effects are the result of exposure to one or several sub-species or classes of VOC.

In this current study, it is unknown whether the observed health effects are due to a specific pollutant or co-exposure to a combination of pollutants, including one or several sub-species of VOC. Greater understanding of the effects of pollutant mixtures, including potential synergism between PM and gaseous or vapour-phase pollutants (such as ozone) is necessary. Additionally, further research that considers atmospheric chemistry including emission sources and incorporating multipollutant models are required.

Finally, further research should also focus on the more extensive measurement of UFP exposure. Since their smaller diameter are considered potentially more damaging to human health at a systematic level than the larger particles, and available evidence investigating the effects of UFP exposure on sub-clinical cardiometabolic outcomes is limited (Ohlwein et al., 2019), future studies should focus on clarifying the role UFP play in instigating harmful systemic effects.

5.5 Clinical implications and relevance of this research

The findings of this research provide plausible evidence to support that exposure to present day, low-level concentrations of indoor air pollution such as that encountered during typical daily activity, might be capable of provoking adverse pathophysiological reactions known to promote cardiometabolic events. Importantly this has been demonstrated in a healthy adult population at concentrations considered 'safe' by ambient air pollution standards, and whilst our findings might be generalizable to a large section of the population, it is known that all

individuals' are not equally responsive to air pollution exposure (Mao et al., 2020; McGuinn et al., 2019; Sacks et al., 2010).

Although we only observed relatively small degrees in some effects, these effects are noted to pose some risk for apparently healthy people and when applied to large populations, even a small change in a health parameter may have substantial public health impact (Riant et al., 2018; Yitshak Sade et al., 2016). These responses could also very conceivably occur in an amplified manner where there are pre-existing cardiometabolic risk factors or conditions that negatively affect the ability to offset against established physiological dysfunction such as autonomic nervous system imbalance, reduced arterial compliance or alterations to vascular tone due to air pollution mediated inflammation. This has already been seen in studies where hypertensive individuals have displayed exaggerated unfavourable effects on BP with exposure to ambient PM when compared to normotensives (Auchincloss et al., 2008), arterial stiffness (potentially air pollution exposure mediated) has shown to augment progression to hypertension in normotensive individuals (Arnett et al., 2001; Clark et al., 2019; D. Liao et al., 1998; Zanoli et al., 2017), and diabetics have shown a heightened risk for air pollution mediated endothelial dysfunction (causing increased risk of macrovascular and microvascular complications) than healthy individuals (Marie S. O'Neill et al., 2005).

This research therefore provides credible rationale and the incentive to follow the lead of several international nations, for the development of Australian IAQ guidelines, which are designed to optimally protect the health of all. Resulting air pollution guidelines should also consider addressing the importance of domestic IAQ on indicators of cardiometabolic risk and application to future public health policy.

CHAPTER SIX – CONCLUSION

In conclusion, the findings of this exploratory study have evidenced significant associations between exposure to commonly encountered concentrations of some domestic indoor pollutants with sub-optimal outcomes related to cardiometabolic risk. Historically air pollution exposure has been implicated as a risk factor for respiratory illness however this view is now challenged by the findings from this and other studies indicating its potential for impacting other distant organs such as the heart, vessels and kidneys.

The pervasive, persistent and unavoidable exposure to ambient air pollution combined with the significant contribution of residential exposure make it a critical factor of cardiometabolic health at the public health level, and is potentially comparable to the other known key risk factors for CVD and diabetes (Rao et al., 2015).

Despite substantial and significant advances in understanding of air pollution exposure and its associated health effects, large gaps in knowledge and important questions persist. To address these gaps and guide prevention, an expanded research agenda needs to be implemented that is translational and incorporates the range of associated disciplines such as exposure science including atmospheric chemists, epidemiology, data linkage and analytics, health policy, and economics (Afsar et al., 2019; Landrigan, Fuller, Hu, et al., 2018).

Overall, these study results strengthen the justification for environmental regulations on domestic air pollutants and efforts to lessen exposure to domestic air pollution should be urgently increased and reinforced by relevant and effective legislation. Furthermore, it is important that policies aimed at lessening levels of outdoor or indoor pollutants are reviewed post hoc for their usefulness in achieving their anticipated aim and improving population health outcomes.

Finally, residential indoor air pollution exposure should be considered as one of several modifiable risk factors in the prevention and management of cardiovascular and metabolic disease and from a public health perspective, the findings presented here are relevant and merit further investigation.

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APPENDICES

Appendix A: Ethics approval

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863

Facsimile +61 8 9266 3793

Web research.curtin.edu.au

19-Sep-2016

Name: Krassi Rumchev

Department/School: Department of Health, Safety and Environment

Email: K.Rumchev@exchange.curtin.edu.au

Dear Krassi Rumchev

RE: Ethics approval
Approval number: HRE2016-0308

Thank you for submitting your application to the Human Research Ethics Office for the project **Associations between domestic indoor air quality and cardiometabolic risk factors**.

Your application was reviewed through the Curtin University low risk ethics review process. The review outcome is: **Approved**.

Your proposal meets the requirements described in National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*.

Approval is granted for a period of one year from **19-Sep-2016** to **18-Sep-2017**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Rumchev, Krassi	CI

Reid, Christopher	Supervisor
Huxley, Rachel	Supervisor
Zhao, Yun	Supervisor
Gilbey, Suzanne	Student
Soares, Mario	Supervisor

Standard conditions of approval

1. Research must be conducted according to the approved proposal

2. Report in a timely manner anything that might warrant review of ethical approval of the project including: proposed changes to the approved proposal or conduct of the study unanticipated problems that might affect continued ethical acceptability of the project major deviations from the approved proposal and/or regulatory guidelines serious adverse events

3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)

4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project

5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised

6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project

7. Changes to personnel working on this project must be reported to the Human Research Ethics Office

8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy

9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner

10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication

11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements

12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Special Conditions of Approval

None.

This letter constitutes ethical approval only. This project may not proceed until you have met all of the Curtin University research governance requirements.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

Dr Catherine Gangell

Manager, Research Integrity

Appendix B: Participant information sheet

INFORMATION SHEET FOR PARTICIPANTS

Dear Participant,

We would like to invite you to participate in a study titled '***ASSOCIATIONS BETWEEN DOMESTIC INDOOR AIR QUALITY AND CARDIOMETABOLIC RISK FACTORS'*** being conducted by researchers from Curtin University. This study aims to investigate domestic indoor air pollution and its relationship with selected cardiometabolic risk factors. To do this, we are looking for non-smokers who are between 35 – 69 years, live in a non-smoking household, who do not have cardiovascular disease, diabetes or chronic respiratory conditions, and are not using blood pressure or cholesterol/lipid lowering medications.

This research project aims to improve our knowledge about the possible link between pollutants, which may be present in indoor and outdoor air, and the development of chronic diseases such as cardiovascular disease and Type 2 diabetes. Some of the types of pollutants we are interested in come from sources such as gas cooking and heating, cleaning products, new furniture and carpets, and traffic pollution.

There are two (2) stages in this research project:

- The first stage involves completing questionnaires, which will give us information about your health history and status, and your home environment including potential sources of air pollutants. The completion of the questionnaires should take about 10 minutes.
- The second stage is divided into two further stages, and involves indoor and outdoor air monitoring and a medical assessment.

Air Monitoring

Air inside and outside your home will be measured. Air samples will be collected from the living room using several pieces of equipment (each about the size of an iPad and contained on a trolley). A researcher will visit your home to set up the sampling equipment and will then return 24 hours later to collect it. Air quality will be measured and recorded by the equipment over the 24-hour period. A blood pressure monitor will also be fitted for you to wear at home, and blood pressure (BP) and heart rate (HR) measurements will be obtained at 30-minute intervals for the same 24-hour period as the

air is being monitored in your house. You will be asked to continuously wear the blood pressure cuff over the 24-hours, and you may experience mild discomfort as the blood pressure cuff inflates to take a measurement. A BP measurement takes about 30 seconds. Each visit by the researcher should not take longer than 25 minutes. We will also ask if you could fill out an activity diary so we know how much time you spent indoors and outdoors during this monitoring period

Medical Assessment

Participants will be invited to attend the clinical health laboratories at Curtin University where resting BP, HR and arterial pulse waves will be measured following a period of five minutes rest. During arterial pulse wave analysis (including arterial pulse wave velocity), you will be asked to wear a thigh blood pressure cuff and have your pulse waves measured from your carotid artery (in your neck) using a small instrument similar to a pencil-sized ultrasound probe. This assessment is non-invasive, although you may experience some mild discomfort whilst the thigh cuff is inflated to take the measurement.

Participants will be asked to fast prior to the medical assessment (for 10-12 hours - water and medications are fine). Also during this visit, participants will be invited to give 40 µL of blood. This is taken from two finger-prick tests and the amount of blood required is that of a small capillary tube. During the finger-prick test, you may experience some mild discomfort. Your lipid and glucose profiles will be ascertained from this blood sample. This gives us information about your cholesterol and glucose levels.

You will also be asked to provide a urine sample, which will give us information about your kidney function.

Lastly, during this visit to the health laboratories, we will measure your weight, height, BMI, waist and hip circumference.

We would be grateful if you would be prepared to take part in all stages and indicate your willingness by completing both the consent form and the questionnaire/s. In all stages the information you provide will be kept confidential and will only be used for research purposes. The results will be presented in an aggregated form so individual participants cannot be identified.

The air quality and medical assessment will not involve any cost to you, and the results will be made available to you. Your involvement in this research is entirely voluntary and you are free to withdraw at any time.

Each participant will also be entered into a final draw to win an iPad. One participants name will be drawn randomly at the completion of the study. Each participant will have one chance, and the same chance as all other participants to win the iPad.

Finally, thank you for your interest and your assistance would be highly appreciated. If you have any further queries, please do not hesitate to contact one of our Researchers:

Curtin University Human Research Ethics Committee (HREC) has approved this study (HREC number HRE2016-0308). Should you wish to discuss the study with someone not directly involved, in particular, any matters concerning the conduct of the study or your rights as a participant, or you wish to make a confidential complaint, you may contact the Ethics Officer on (08) 9266 9223 or the Manager, Research Integrity on (08) 9266 7093 or email hrec@curtin.edu.au.

Principal Investigator:

Dr Krassi Rumchev. PhD, MSc

Tel: (08) 9266 4342

Researcher:

Ms Sue Gilbey. PhD Candidate.

Email: sue.gilbey@curtin.edu.au

Appendix C: Consent form

Location ID:

FORM OF CONSENT

I,.....
Given names Surname

have read the information sheet explaining the details of the study titled '***ASSOCIATIONS BETWEEN DOMESTIC INDOOR AIR QUALITY AND CARDIOMETABOLIC RISK FACTORS***'

I agree to participate in this study and understand that my withdrawal from the study at any stage will not negatively affect me in any way.

I consent to the collation of my data with that of others for the purposes of data analysis and write up towards scientific journals. I have been given an opportunity to ask questions of the investigators and have been assured that my personal details will not be released to anyone outside this investigating group, and that stored data will be de-identified.

Date.....

PARTICIPANT'S SIGNATURE .....

WITNESS SIGNATURE .....

Appendix D: Health Survey

Location

Screening and Health Survey

Project Title: Associations between domestic indoor air quality and cardiometabolic risk factors

Thank you for your interest in this research program. This study has been approved by the Curtin University Human Research Ethics Committee (Approval number: HRE2016-0308). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either in writing to the Curtin University Human Research Ethics Committee c/- Office of Research Development, Curtin University of Technology, GPO Box U1987, Perth 6845, or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Purpose of study: You are invited to participate in this study which aims to investigate whether indoor air pollution is related to selected risk factors associated with chronic conditions such as cardiovascular disease and type 2 diabetes. These outcomes will be compared to previous published literature.

Screening Survey: In order for us to determine your suitability for our program, we invite you to kindly fill in this short survey. This form can also be filled in online and will take approximately 5 minutes. There are no known risks in filling this application.

Confidentiality: Any information that you provide to us regarding your identity, will be de-identified before being stored securely, to protect your privacy.

Please place a cross (X) in the box to indicate you have read and understood what is required of you in this survey, and that you are willing to participate.

Proceed to the survey

Please complete the spaces as indicated below. Please place a **cross (X)** in the box that corresponds to your answer. If your response is YES to any question, you may provide further details in the space provided.

Demographics

First name: _____

Last name: _____

Address: _____

Suburb: _____

Postcode: _____

Telephone: _____(home)

_____ (mobile)

Email _____

Date of Birth: _____ Age:_____ years

Country of Birth: _____

Duration lived in Australia: _____(years).

Parents' country of birth:

Father: _____ & Mother:_____

Health Survey

1. Are you currently a smoker? Y ☐ N ☐

2. Do you have more than 2 alcoholic drinks per day? Y ☐ N ☐

3. Has your weight fluctuated by 3 (or more) kg in the last 6 months

Y ☐ N ☐

4. Do you plan on trying to lose weight in the next 6 months?

Y ☐ N ☐

Females only:

Menopause status: PRE PERI POST

Are you pregnant or planning to be pregnant in the next 6 months?

Y ☐ N ☐

Are you breastfeeding or plan to breastfeed in the next 6 months?

Y ☐ N ☐

5. Do you suffer from any of the following chronic diseases/other health conditions?

a) Diabetes Y ☐ N ☐

b) Asthma Y ☐ N ☐

c) Other chronic respiratory disease Y ☐ N ☐

d) Cardiovascular disease Y ☐ N ☐

e) Kidney disease Y ☐ N ☐

f) Kidney stones (more than 2) Y N

g) Thyroid condition/disease Y ☐ N ☐

h) High blood lipids (triglycerides, cholesterol) Y ☐ N ☐

i) High blood pressure Y N

☐ ☐

j) Have you ever had a heart attack or suffered from chest pain needing hospitalization? Y ☐ N ☐

Other chronic diseases or health conditions? Please provide details below;

6. Are you currently on any medications or any vitamin supplementation?

a) Blood pressure lowering medication Y ☐ N ☐
b) Cholesterol lowering drugs Y ☐ N ☐
c) Hormone replacement therapy Y ☐ N ☐
d) Steroids Y ☐ N ☐
e) Vitamin Supplements (Vitamin D in particular) Y ☐ N ☐
f) Weight loss pills Y ☐ N ☐
g) Any other medicines? Y ☐ N ☐

Please provide details of medications you are taking below;

Thank you for your participation!

Appendix E: Domestic environment survey

Location ☐

Home Environment Questionnaire

Name _____

Address _____

_____

Date questionnaire completed _____

****

The questions in this section relate to your home environment.

Could you please answer the questions by placing a cross (X) in the most appropriate box.

1. Does anybody smoke inside the house? Y ☐ N ☐
2. What type of heating do you use in **Winter**?

   (Please select more than one if appropriate)

a) Reverse cycle air-conditioning……. ☐

b) Gas heater
   a. Flued……. ☐
   b. Unflued…….. ☐

c) Electric heater/appliance…….. ☐

d) Wood heater
   a. Open fire……. ☐
   b. Closed fire…… ☐

e) Oil heater……... ☐

f) Other, please specify……..

……

g) No heating…… ☐

3. Please estimate the number of hours (on average) you would use heating during the day in **Winter** (no of hours):_____

4. How frequently would you 'air' your house (i.e. open lots of windows) in **Winter**?

   a) Daily…… ☐
   b) Weekly…….. ☐
   c) Monthly……. ☐
   d) Rarely……. ☐
   e) Never……. ☐

5. What type of cooling do you use in **Summer**?

   (Please select more than one if appropriate)

   a) Air conditioning
      a. Refridgerative……. ☐
      b. Evaporative……. ☐

Is the air conditioning -

i. Central/whole house system…… ☐
ii. Split system in bedroom…… ☐
iii. Split system in living room……. ☐

b) Portable fan…….. ☐
c) Ceiling/wall fan…….. ☐
d) Evaporative cooler…… ☐
e) Other, please specify……
……..
f) No cooling…….. ☐

6. Please estimate the number of hours (on average) you would use cooling during the day in **Summer** (no of hours):_____

7. How frequently would you 'air' your house (i.e. open lots of windows) in **Summer**?

f) Daily…… ☐
g) Weekly…….. ☐
h) Monthly……. ☐
i) Rarely……. ☐
j) Never……. ☐

8. Which of the following are regularly done in this house?
   a) Dry clean furnishings……. ☐
   b) Wash/dry-clean curtains……. ☐
   c) Clean carpets…….. ☐
   d) Don't do any of these things…… ☐

9. Which of the following best describes how often you vacuum/mop/sweep the floors/carpets;

a) Daily…… ☐
b) Few times/week…… ☐
c) Few times/month…… ☐
d) Once/month…… ☐
e) Less than once/month…… ☐
f) Never……..... ☐

☐ ☐

10. Do you use any special house cleaning materials? Y N

If yes, please specify:

11. How would you describe the general ventilation of your home?

	In bedroom	In living Room
a) Very good……	☐ ……..	☐
b) Good……	☐ ……	☐
c) Poor……	☐ ……	☐

12. Are your cooking appliances:

a) Gas……. ☐
b) Electric…… ☐
c) Both……. ☐

13. On average how many times per week do you use your stove?

…….times per week.

14. How long is an average cooking period?

…….length of time

15. How regularly do you use an extractor fan when cooking?

a) Always……. ☐
b) Sometimes…… ☐
c) Never……. ☐
d) No extractor fan installed……. ☐

16. Do you have a garage that is attached to the home? Y ☐ N ☐

17. What is the distance of your house from a major roadway?

a) Within 50m…… ☐
b) Within 100m…… ☐
c) Greater than 300m…… ☐

18. What is the distance of your house from an industrial area?

a) Within 50m…… ☐
b) Within 100m…… ☐

c) Greater than 300m…… ☐

19. What kind of floor coverings do you have?

	In bedroom	In living Room
a) Carpet……	☐	☐
b) Ceramic……	☐	☐
c) Linoleum……	☐	☐
d) Concrete……	☐	☐
e) Slate (stone) ……	☐	☐
f) Parquet……	☐	☐
g) Solid timber……	☐	☐
h) Laminated timber……	☐	☐
i) Other……	☐	☐

20. During the last 3 months, have any of the following taken place?

a) New carpeting……. ☐
b) Walls painted……. ☐
c) New furniture……. ☐
d) New wall covering (other than painting) …… ☐

21. How old is your house?

a) Less than 5 years old……. ☐
b) Between 5 and 10 years old…… ☐
c) Greater than 10 years…… ☐

22. How many people live in the house?..... ☐

23. How many bedrooms do you have?..... ☐

THANK YOU FOR YOUR PARTICIPATION

Appendix F: Time-activity diary

Location

You will now be wearing the blood pressure monitor and there will be equipment in your home measuring the air quality.

During this time it would be much appreciated if you could tell us what you were doing over this 24-hours.

Please circle the activity that best describes what you were doing.

Please also circle the time you start recording.

Time - Activity Diary

1) What time did you go to bed?_____
2) What time did you get up in the morning? _____

Diary

5 am – 6 am Indoors Outdoors Home Work

What were you doing?

6 am – 7 am Indoors Outdoors Home Work

What were you doing?

7 am – 8 am Indoors Outdoors Home Work

What were you doing?

8 am – 9 am Indoors Outdoors Home Work

What were you doing?

9 am – 10 am Indoors Outdoors Home Work

What were you doing?

10 am – 11am Indoors Outdoors Home Work

What were you doing?

11 am – 12 noon Indoors Outdoors Home Work

What were you doing?

12 noon – 1pm Indoors Outdoors Home Work

What were you doing?

1 pm – 2 pm Indoors Outdoors Home Work

What were you doing?

2 pm – 3 pm Indoors Outdoors Home Work

What were you doing?

3 pm – 4 pm Indoors Outdoors Home Work

What were you doing?

4 pm – 5 pm Indoors Outdoors Home Work

What were you doing?

5 pm – 6 pm Indoors Outdoors Home Work

What were you doing?

6 pm – 7 pm Indoors Outdoors Home Work

What were you doing?

7 pm – 8 pm Indoors Outdoors Home Work

What were you doing?

8 pm – 9 pm Indoors Outdoors Home Work

What were you doing?

9 pm – 10 pm Indoors Outdoors Home Work

What were you doing?

10 pm – 11 pm Indoors Outdoors Home Work

What were you doing?

Any other comments?

Thank you – your participation is much appreciated!!

Appendix G: Clinical assessment

Health screening assessment

ID:_____

Name:_____

_____

Date: _____ Time: -

_____

Time and date of last meal:_____ Fasting:

Yes / No

DOB:_____

Anthropometrics

Height: _____m [_____ m^2]

Weight: _____kg

BMI: [weight (kg)/ height^2 (m^2)] : _____(2 decimal places)

Waist measurement: _____cm

Hip measurement: _____cm

Waist / hip ratio: waist circumference (cm) / hip circumference (cm): _____

BP: **HR:**

LEFT ARM

1st _____/_____ mmHg _____

2nd _____/_____ mmHg _____

3rd _____/_____ mmHg _____

Avg: BP: _____/_____ mmHg HR: _____

RIGHT ARM

BP: **HR:**

1st _____/_____ mmHg _____

2nd _____/_____ mmHg _____

3rd _____/_____ mmHg _____

Avg: BP: _____/_____ mmHg HR: _____

Biochemistry

Lipid profile:

TC: _____ mmol/L

HDL: _____ mmol/L

Chol: _____ mmol/L

Trig: _____ mmol/L

LDL: _____ mmol/L

Non-HDL: _____ mmol/L

TC/HDL: _____

Glucose profile:

Glucose: _____ mmol/L

HbA1c: _____ %

Renal function:

Alb: _____ Creatinine: _____

Alb/Cr ratio: _____

SphygmoCor PWA and PWV results sheet

Pulse Wave Analysis (PWA)

Non-dominant arm LEFT / RIGHT Cuff size: Standard / Large

Height: _____cm

Date of birth: _____

BP1:_____ BP2:_____ BP3:_____

_____

Average brachial BP: _____

Central BP: _____

MAP_____ HR _____

SP_____ PP _____

AP_____ Aix75 _____

Pulse Wave Velocity (PWV)

Carotid to sternum measurement: _____mm

Sternum to top of leg cuff measurement: _____mm

Top of leg cuff to groin measurement: _____mm

PWV distance: _____mm BP: _____mmHg

Reading1 Reading2 Reading 3

HR _____

PWV (m/s) _____

Pulse transit time _____

Assessor: _____ _____