Aspects of cardiovascular risk in an Australian population study

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A thesis with publications submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all of the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Thanh-Binh Nguyen-Duy

Tuesday, 13th November 2018

ACKNOWLEDGEMENTS

I am very happy to be writing this part of my thesis as it means that I have come this far in my PhD journey. I have truly enjoyed the whole journey and as I like to say, this has been one of my favourite degrees! While there are several reasons for this, the people that have helped me and encouraged me along have made a meaningful difference. I would like to thank both of my wonderful supervisors, Melody and Adrian, for seeing potential in me and approaching me with the idea of undertaking a PhD. Your passion and dedication to research that matters to you are inspiring to those around you. I always felt well supported by both of you; even when you were traveling across the globe, I knew that I could count on you! Melody, I could not have asked for a better primary supervisor-student match, our styles complemented each other effortlessly. Thank you for your trust and giving me the space and independence to grow as a researcher and to explore questions that matter to me. Thank you also for wisely knowing when to provide guidance, always looking out and creating opportunities for me, and being a wonderful mentor and friend. I am so glad that our paths crossed a few years ago and that they will continue to do so in the future. I feel extremely lucky to have had you as my primary supervisor – you were truly amazing! Adrian, thank you for giving me the opportunity to work at the Prevention Research Collaboration and encouraging me to get in touch with you after being on maternity leave. I will always remember our first meeting where you drew different things on a notepad to try to figure out what type of research would interest me. That gave me a bit of insight into the wonderful way your mind works and a taste of meetings to come. All of your input has been insightful and instrumental, and has helped to further enhance the quality of research undertaken during my PhD. I have enjoyed learning from all of our interactions – thank you for sharing your wisdom and for being there for me during the final dash to finish my thesis.

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ABBREVIATIONS

ABS	Australian Bureau of Statistics
ACM	All-cause mortality
AIHW	Australian Institute of Health and Welfare
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
DALYs	Disability Adjusted Life Years
HDL	High-density lipoprotein
HT	Hypertension
LDL	Low-density lipoprotein
MI	Myocardial infarction
NCD	Non-communicable disease
NSW	New South Wales
PA	Physical activity
SEEF	Social, Economic, and Environmental Factor Study
US	United States
WHO	World Health Organization
YLL	Years of Life Lost

ABSTRACT

Prevention of cardiovascular disease (CVD), a leading cause of death in men and women, is both a global and national public health priority. Prevention efforts have generally focused on well-known lifestyle (e.g., physical inactivity, unhealthy diet, smoking) and metabolic (e.g., overweight/obesity, hypertension, hyperlipidaemia) risk factors. It is also important for public health strategies to consider emerging risk factors, innovative approaches to risk factors, and evidence in middle-aged men and women, to develop effective prevention strategies.

This thesis explored innovative aspects of cardiovascular risk in a large cohort of middle-aged and older Australian men and women ("the 45 and Up Study") by examining: 1) emerging or lesser known risk factors such as raw vegetable intake (**Chapter 3**), sedentary behaviour (**Chapter 4, Appendix 1**) and psychological distress (**Chapter 5**); 2) the single versus joint influence of lifestyle risk factors on incident type 2 diabetes (**Chapter 4, Appendix 1**) and hypertension (**Chapter 5**); 3) potential gender differences (**Chapters 3-5, Appendix 1**), and female-specific behaviours such as breastfeeding (**Chapters 6-7**).

Overall, findings support Australian recommendations for fruit and vegetable intake, physical activity, alcohol intake and infant breastfeeding. While the importance of reducing known risk factors for CVD prevention was evident, the role of raw vegetable intake, sedentary behaviour and psychological distress was inconclusive. Breastfeeding was associated with a lower maternal risk of CVD. Findings confirmed that adopting a cluster of healthy lifestyle behaviours can reduce CVD risk in the middle-aged and older population. Potential gender differences were explored and identified. This thesis contributes to the literature by exploring innovative aspects of cardiovascular risk that are relevant to middle-aged adults, particularly women, as well as informs health care providers, researchers and policy makers.

CHAPTER ONE: Thesis overview

1.1 BACKGROUND

Cardiovascular disease (CVD) refers to diseases of the heart and blood vessels. It is the leading cause of death globally and is responsible for a third of deaths worldwide.[1] Despite significant reductions in deaths from CVD in high-income countries in the last four decades, CVD remains the leading cause of death in developed countries, including Australia.[2] As CVD is substantially preventable, public health efforts and guidelines worldwide have focused on prevention strategies aimed at improving healthy lifestyle behaviours in both populations and individuals.[3] Even modest changes in lifestyle risk factors can lead to substantial reduction in the risk of CVD mortality.[4] According to the World Health Organization (WHO), up to 80% of premature heart disease and stroke could be prevented by a healthy lifestyle.[5] The four major behavioural risk factors include physical inactivity, an unhealthy diet, tobacco smoking, and excessive alcohol consumption.[6] These can lead to metabolic or physiological changes, or intermediate risk factors of developing CVD, including overweight/obesity, hypertension, hyperlipidaemia, hyperglycaemia and diabetes.[6]

Prevention efforts and research have historically focused on these well-established lifestyle and physiological risk factors. In recent years, these factors have been explored from new research angles, generating additional knowledge about how these factors may relate to CVD. There is also growing evidence for associations between emerging lifestyle risk factors, such as sedentary behaviour, and CVD, that highlight the potential importance of lesser known factors. CVD is a complex disease that arises not from one, but several causes which can occur in multiple combinations and interact with each other.[7] As evidence continues to grow, it is important for researchers to consider innovative aspects of cardiovascular risk to improve understanding of how lifestyle/metabolic risk factors contribute to CVD, and to continually inform prevention strategies.

Global efforts, including prevention strategies targeting risk reduction, have been dedicated to reducing premature deaths from CVD. The United Nations (UN) and WHO have been the main drivers behind a global commitment to reduce premature deaths from four main non-communicable diseases (NCDs) including CVD, by a relative 25% from its 2010 levels by the

year 2025.[8] A substantial proportion of deaths and disease burden attributed to CVD occur prematurely before the age of 70,[9] and many of these deaths are preventable. Hence, identifying evidence that can inform prevention approaches involving cardiovascular risk factors in the middle-aged population should be a public health priority.

Another key public health and research priority that deserves attention is cardiovascular risk and CVD prevention in women. While CVD is the leading cause of death among women,[10] historically there has been a general lack of awareness about CVD risk in women, an under-representation of women in cardiovascular research, and a lack of research on women's health.[11,12] Previous research has highlighted gender differences in the epidemiology, symptoms, management and disease outcomes of CVD which need to be further examined.[13] As such, several international and national health bodies with a primary interest in CVD have raised a "red alert for women's heart" to increase awareness about the importance of CVD in women and have urged for more gender-specific research.[13-16] Compared to men, women generally have a later onset of CVD and sometimes present with atypical or under-recognised symptoms which can cause delay in seeking treatment, under-diagnosis of CVD, and a lower likelihood of being referred to appropriate diagnostic and treatment procedures.[17] The effectiveness of treatment may also vary by gender where poorer clinical outcomes have been reported in women, possibly due to poorer psychosocial adjustment or delayed or under-recognition of cardiac conditions among women.[17] With respect to CVD risk factors, while gender difference is observed in the prevalence and incidence of traditional risk factors, such as smoking and physical inactivity,[17,18] women also have their unique risk factors, including reproductive risk factors that could be further explored.[13] Pursuing gender-specific research on cardiovascular risk factors could help inform healthcare providers, the population, and public health programs and policies.

As CVD continues to account for the largest number of deaths worldwide, both prevention and research efforts that focus on cardiovascular risk factors are important. While previous efforts have focused for the most part on known risk factors for CVD such as smoking and physical inactivity, there has been limited research about novel approaches to risk factors, such as examining the joint influence of risk factors rather than examining individual risk factors in isolation. In addition, emerging knowledge about other less traditional lifestyle behaviours, such as sedentary behaviour or breastfeeding in mothers, may also be valuable to consider in CVD prevention strategies. Therefore, the aims of this thesis are to explore less well researched

aspects of CVD prevention, within the context of the 45 and Up Study, an Australian population study involving middle-aged and older men and women. This thesis also provides an example of using an Australian population cohort in thematically linked cardiovascular research. This thesis is innovative because: 1) it examined less established cardiovascular risk factors, including raw vegetable consumption, sedentary behaviour and poor mental health; 2) it applied novel methodologies in several studies by comparing the single and combined influence of multiple lifestyle risk factors; and 3) of its consideration of gender by either examining potential gender differences or focusing on cardiovascular risks of behaviours specific to women, such as breastfeeding.

1.2 PURPOSE AND SIGNIFICANCE OF THE RESEARCH

The purpose of this thesis is to gain a deeper understanding of the relationship among innovative cardiovascular risk factors principally in a large cohort study of middle-aged and older Australian adults. Findings from this research can significantly contribute to the evidence base for chronic disease prevention, particularly in relation to CVD, and help inform public health recommendations on innovative cardiovascular risk factors in both men and women. The specific aims of this research are to examine:

1. The relationship between the consumption of fruit and vegetables (considered separately or combined) and mortality from all causes, with an innovative examination of the influence of raw versus cooked vegetables (**Chapter 3**);
2. The separate and combined influence of overweight/obesity, physical activity, and sedentary behaviour on the development of type 2 diabetes, a strong risk factor for CVD (**Chapter 4, Appendix 1**);
3. The separate and combined influence of six lifestyle risk factors, including known and lesser known lifestyle risk factors, on the development of hypertension, the most important single risk factor for CVD (**Chapter 5**);
4. The relationship between breastfeeding and maternal cardiovascular risk factors and outcomes (both as a systematic review [**Chapter 6**] and a longitudinal study [**Chapter 7**]);

5. Potential differences between women and men in all of the above examined relationships involving innovative angles of cardiovascular risk (**Chapters 3-5, Appendix 1**), in a large Australian cohort of adults aged 45 years and over.

1.3 THESIS OUTLINE

This thesis comprises eight chapters and presents findings relating to five peer-reviewed papers (four published, one in press). Collectively, the studies presented in this thesis (**Chapters 3-7**) explore less well researched aspects of cardiovascular risk including dietary (**Chapter 3**), metabolic (**Chapters 4-6**), and gender-specific risk (**Chapters 3-7**), mainly in a large Australian cohort of middle-aged and older adults from the "45 and Up Study" (**Chapters 3-5, 7)**. An overview of innovative aspects of cardiovascular risk examined in this thesis, and chapters/appendices relating to cardiovascular risk factors considered, is presented in **Figure 1.1**. An outline of the thesis is presented below.

Chapter 1 provides a brief background to the research undertaken in this thesis and outlines the research project's novelty, purpose, significance, and the structure of the thesis.

Chapter 2 presents an overview of the literature relating to CVD and risk factors for CVD, including innovative ones examined in this thesis.

Chapter 3 describes findings from a peer-reviewed paper investigating the relation between individual and combined fruit and vegetable consumption and all-cause mortality in the 45 and Up Study cohort. In addition, we further addressed the lesser known question regarding the consumption of raw versus cooked vegetables in relation to mortality risk.

Chapter 4 presents findings from a peer-reviewed paper examining the combined influence of overweight/obesity, physical activity, and sedentary behaviour (an emerging risk factor) on the incidence of type 2 diabetes among 45 and Up Study participants. The joint influence of these three lifestyle risk factors on incident type 2 diabetes has infrequently been studied.

Chapter 5 provides findings from a peer-reviewed paper that examined the individual and combined influence of known and lesser known lifestyle risk factors (e.g., psychological distress)

on the incidence of hypertension among 45 and Up Study participants. In this study, we developed a novel lifestyle risk score for summarising hypertension risk.

Chapter 6 describes findings from a peer-reviewed systematic review of the relationship between breastfeeding and maternal cardiovascular risk factors and outcomes that have not been previously systematically synthesised, such as metabolic syndrome, hypertension and CVD. This study identified the need for additional longitudinal studies examining the association between breastfeeding and cardiovascular risk factors and outcomes.

To address this research gap, **Chapter 7** describes findings from a study exploring the association between breastfeeding and the incidence of CVD-related hospitalisation and CVD mortality in the 45 and Up Study cohort.

Chapter 8 provides an overarching discussion of the significance of the main findings from studies presented in this thesis, implications for policy, and directions for future research.

More detailed information about the 45 and Up Study is presented in the manuscripts featured in **Chapters 3-5** and **7**. Briefly, the 45 and Up Study is the largest prospective cohort study in Australia involving 267,153 men and women aged 45 years over, that were randomly sampled from the New South Wales (NSW) population. The cohort represents about 10% of the NSW population aged 45 years and over. The 45 and Up Study is a unique resource for researchers that provides information on a wide range of exposures and outcomes of public health relevance and linkage to routinely collected health data from a variety of population databases and registries. Linkage data include hospital data from the NSW Admitted Patient Data Collection (APDC; until June 2014), mortality data from the NSW Registry of Births, Deaths, and Marriages (until June 2014), and data on causes of death from the Cause of Death Unit Record File (until December 2013) by the Centre for Health Record Linkage (CHeReL) using highly accurate probabilistic record linkage methods and a commercially available software (Choice-Maker, ChoiceMaker Technologies Inc.). From 2006 to 2008, participants joined the study by completing a mailed questionnaire and providing informed consent. In 2010, the first 100,000 participants to complete the baseline questionnaire of the 45 and Up Study were invited to participate in the Social, Economic and Environmental Factor (SEEF) Study follow-up (response rate of 60.4%). The 45 and Up Study and the SEEF Study provided baseline and follow-up data for studies presented in **Chapters 4** and **5**. Originally, I had planned to include CVD outcomes in studies presented in

Chapters 3 to 5 as these data were supposed to be available at the start of my thesis, as promised by the SAX Institute. However, update of data linkage was significantly delayed and CVD outcomes were not available at the time of analysis. All-cause mortality was therefore used as the outcome in **Chapter 3**; incident type 2 diabetes and hypertension, both strong risk factors for CVD, were used as the outcomes for **Chapters 4** and **5**, respectively. The 45 and Up Study baseline data and linked CVD hospitalisation and/or mortality data were used in studies presented in **Chapters 3** and **7** as hospitalisation and cause of death data became available from January 2018 onwards. The difference in outcomes has also resulted in differences in statistical methods, where logistic regression was used for incidence data in **Chapters 4** and **5**, and Cox proportional hazards models were used for **Chapters 3** and **7** where time-to-event outcomes were available.

Additional material that is relevant to studies presented in this thesis or supplementary material to support the thesis has been included in the **Appendices**. In **Appendix 1**, findings from an additional gender analysis that complements findings from the published paper included in **Chapter 4** are presented. Both the baseline 45 and Up Study and SEEF follow-up questionnaires are included as **Appendices 2** and **3** respectively. Additional research dissemination arising from this thesis and additional peer-reviewed papers that were published during the PhD candidature are described respectively in **Appendix 4** and **Appendix 5**.

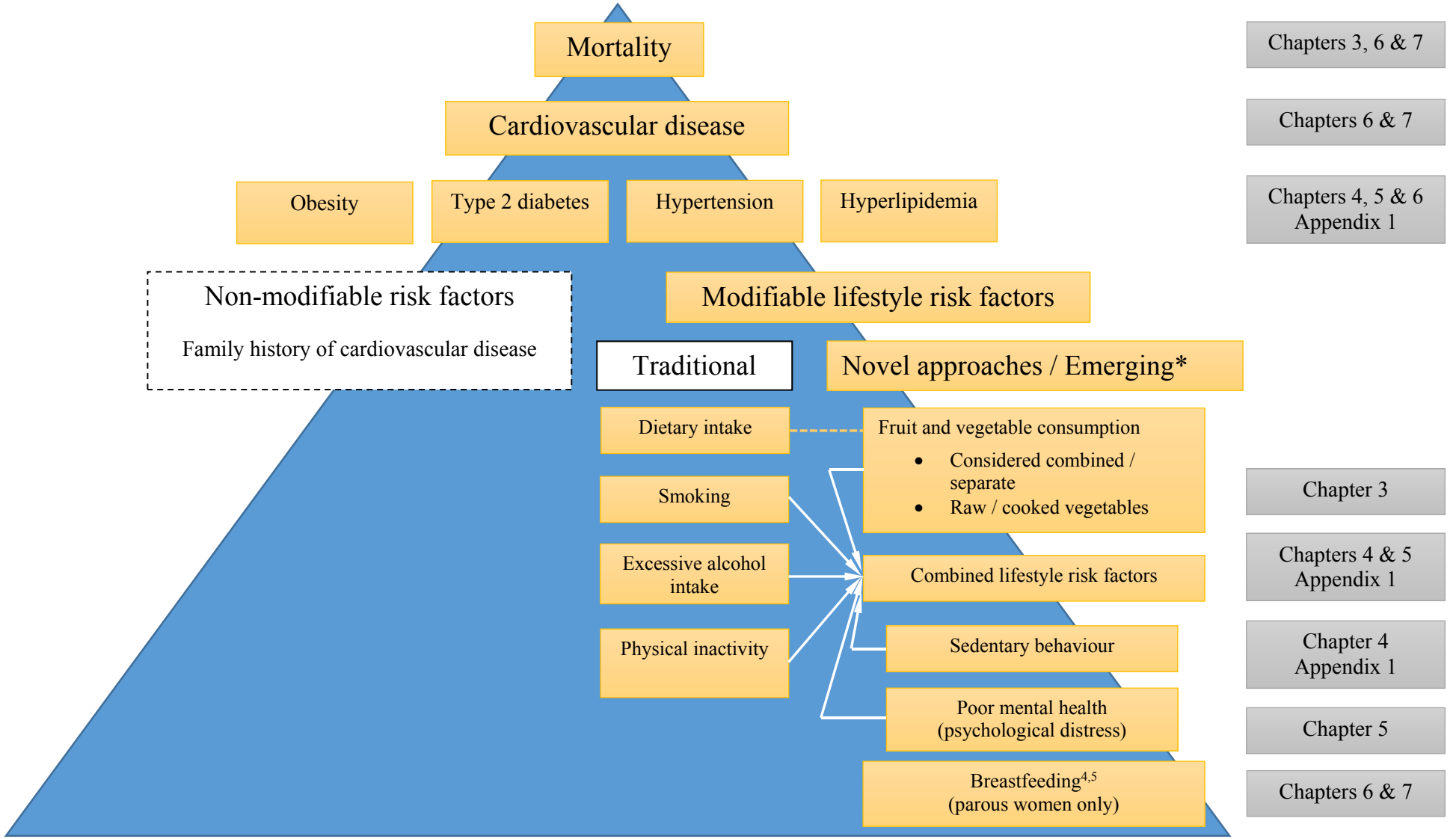

Figure 1.1. Overview of innovative aspects of cardiovascular risk examined in this thesis.

Figure legend

*	"Novel approaches" refer to new approaches to lifestyle risk factors, while "emerging" refers to recently identified lifestyle risk factors that may have important associations with cardiovascular disease, that were considered in this thesis
---	Non-modifiable risk factors were not examined in the current PhD project
Chapter X	Chapter/Appendix number in which the given risk factor/outcome is discussed in this thesis
Smoking	Given risk factor/outcome is examined in this thesis
- - - - - - - -	Only fruit and vegetable intake was considered

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CHAPTER TWO: Review of the literature

2.1 PURPOSE OF THIS REVIEW

This chapter aims to provide a wider context to the research questions explored in this thesis by reviewing literature that is pertinent to the research undertaken and identifying potential research gaps. An overview of CVD, cardiovascular risk factors examined with an innovative angle in this thesis, will be presented, and the importance of CVD prevention both in the middle-aged population and in women.

2.2 CVD STATISTICS: WORLDWIDE AND IN AUSTRALIA

Responsible for 71% of global annual deaths and 91% of Australian deaths in 2014, NCDs including CVD, cancer, chronic respiratory diseases and diabetes define the central global and national public health agendas.[1] CVD is the leading cause of death in the world, accounting for 31% of global deaths or an estimated 17.9 million deaths in 2015, 53% of which occurred in men and 47% in women.[2] CVD is also a major cause of disability, contributing to 15% of total global disease burden (16% in men, 14% in women).[3] Globally, the estimated prevalence of CVD was 423 million cases in 2015[2] and its estimated cost was $863 billion US dollars in 2010.[4]

Since the 1960s, there has been a major decline in death rates from CVD as a result of improved prevention, detection, management and treatment of CVD.[5] However, with a growing number of Australians living to an older age, CVD remains a public health challenge in Australia. In 2015, about 4.2 million (22%) Australians reported having CVD, with the prevalence of CVD markedly increasing with age in both women and men (**Figure 2.1**).[6] Despite improvements over the last several decades, CVD remains a leading cause of death and a major cause of hospital admissions in Australia. In 2015, nearly a third of all deaths (30% for females, 27% for males)[7] and 11% of hospitalisations were attributed to CVD, with hospitalisation rates 1.6 times higher in men than in women, and consistently higher in men than in women across all age groups.[6] The age-standardised heart attack rate was 379 per 100,000 people in 2013, with males experiencing more than twice the rate of females (523 versus 246 per 100,000, respectively).[8] CVD has the

second highest disease burden in Australia (based on the number of years of life lost [YLL]; 25.8% of total disease burden) after cancer[9] and is the most expensive group of diseases, costing $7.7 billion annually or 10.4% of the nation's total health care expenditure, with more than half of the costs arising from hospital admissions.[10] As CVD is a leading cause of death, disease burden, and health care cost in Australia and in the world, CVD prevention is both an important national and global health priority.

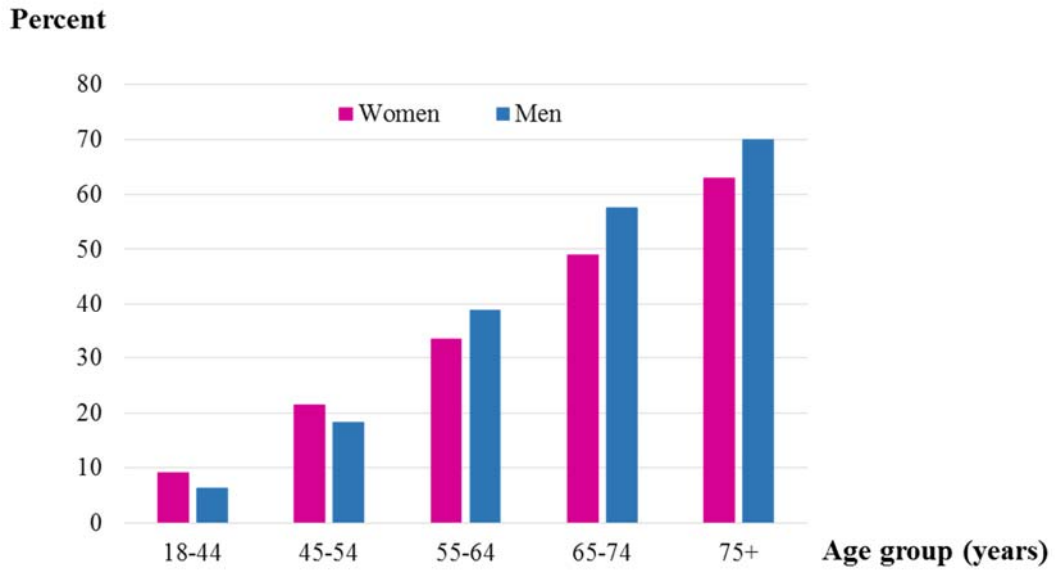

Figure 2.1. Prevalence of self-reported CVD (having one or more types of CVD) in adults by age and sex (2014-15). Adapted from "Cardiovascular disease snapshot" by the Australian Institute of Health and Welfare (AIHW), 2017.[11]

2.3 CVD PATHOGENESIS

2.3.1 Types of CVD

Collectively, CVD refers to diseases of the heart and blood vessels. The main conditions that are relevant to this thesis are summarised in **Table 2.1**.

Table 2.1. Description of types of CVD[a] that are relevant to this thesis.

CVD disease group	Description	Example of diseases within this group
Coronary heart disease (also known as "ischaemic heart disease")	Blood supply to the heart is blocked or reduced due to a gradual build-up of fatty substances in the walls of the coronary arteries. This may result in chest pain or discomfort that can spread into the shoulders, arm, back, neck or jaw ("angina") or a "heart attack" (sudden blood flow blockage causing heart tissue damage)	Stable angina, unstable angina, acute myocardial infarction (or "heart attack"), sudden cardiac death
Cerebrovascular disease (includes stroke)	Blood vessels supplying blood to the brain become blocked (for example by a blood clot; "ischaemic stroke"), malformed, or rupture and bleed ("haemorrhagic stroke")	Stroke, transient ischemic attack, cerebral aneurysm, vascular malformation, stenosis
Hypertensive heart disease	Heart conditions resulting from high blood pressure	Heart failure, heart muscle thickening, coronary artery disease, and other conditions

[a] Other types include peripheral vascular disease, rheumatic heart disease, inflammatory heart disease, and other forms of cardiovascular and circulatory diseases.

The most common types of CVD are coronary heart disease (CHD) and stroke, the leading causes of death and disability worldwide.[12] Combined, CHD and stroke account for more than

85% of CVD deaths worldwide,[12] with an estimated 8.9 and 6.3 million deaths attributed to CHD and stroke respectively, and mortality rates increasing substantially from middle age onwards.[2] CHD is the leading cause of global disease burden, followed by stroke, and then hypertensive heart disease in fourth place.[2] CHD deaths as a proportion of all Australian deaths by age and sex, is represented in **Figure 2.2**. In Australian women, the proportion of CHD deaths increases gradually with age, while in Australian men, the proportion increases at an earlier age and is comparatively higher throughout the years.

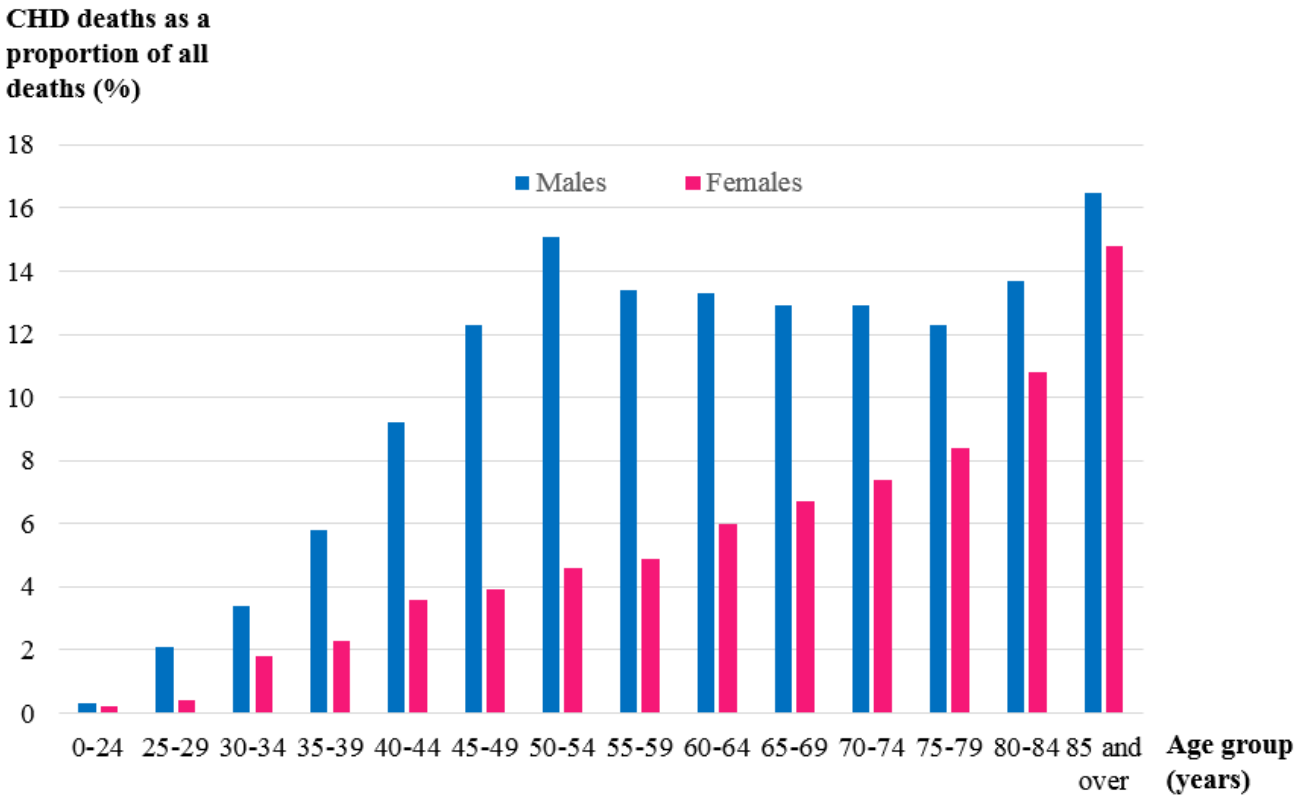

Figure 2.2. CHD deaths as a proportion of all Australian deaths by age and sex. Adapted from "Causes of death, Australia, 2015" by the Australian Bureau of Statistics (ABS), 2017.[13]

The contribution of different types of CVD to global CVD burden in men and women is represented in **Figure 2.3**. In both men and women, CHD and stroke were the largest contributors to CVD burden measured in Disability Adjusted Life Years (DALYs), which provide a measure of healthy years of life lost due to premature mortality and disability. While cerebrovascular

disease, hypertensive heart disease, and other types of CVD, contributed a higher proportion of DALYs to global CVD burden in women than in men, CHD accounted for a greater proportion of global CVD burden in men. For most of the last century, the most important single cause of death in Australia has been CHD. The proportion of deaths attributed to different types of CVD in Australia are presented in **Figure 2.4**. Similarly to data presented in the previous figure, CHD was responsible for a larger proportion of CVD deaths in men than in women. Stroke, hypertensive heart disease, and other types of CVD accounted for a greater proportion of deaths in women than in men. CHD and stroke are both related to lifestyle.

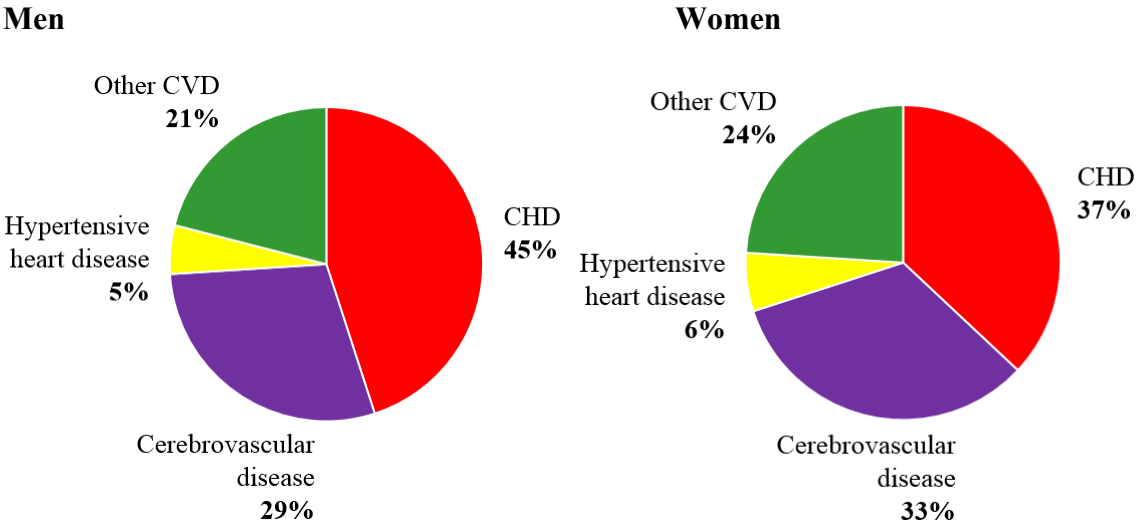

Figure 2.3. **Distribution of global CVD burden (measured in Disability Adjusted Life Years or DALYs) in men and women based on CVD types relevant to this thesis.** Other CVD includes inflammatory heart disease, rheumatic heart disease and other types of CVD. Adapted from "Global atlas on CVD prevention and control", by S. Mendis, P. Puska, and B. Norrving, 2011.[14]

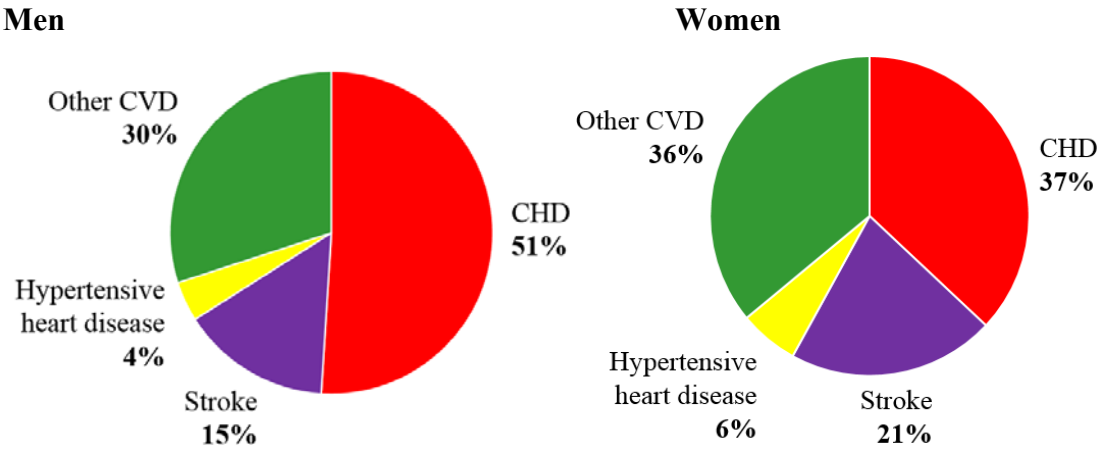

Figure 2.4. **Proportion of CVD deaths in Australian men and women based on CVD types relevant to this thesis.** Other CVD include heart failure, cardiomyopathy, peripheral vascular disease, rheumatic heart disease, and other types of CVD. Adapted from "Heart, stroke & vascular diseases: Data tables: Cardiovascular disease 2018", by the AIHW, 2018.[15]

2.3.2 Atherosclerosis

The main cause of CVD is the progressive narrowing or blockage of arteries, the blood vessels that supply oxygen and blood to the heart and other parts of the body, due to the build-up of fatty deposits ("plaques") on artery walls. This gradual process, known as atherosclerosis, can start at a young age and slowly develop over the years.[16] This progressive disease has several distinct pathologic stages summarised in **Table 2.2** below. The behavioural and metabolic risk factors of atherosclerosis are similar to those for CVD (presented in section 2.4.1.2 of this chapter).

Table 2.2. Summary of the three distinct pathologic stages of atherosclerosis.

Pathologic stage	**Description**
Fatty streak formation	Endothelial cells line blood vessels and facilitate exchanges between the blood and surrounding tissues.

	Endothelial damage: The endothelial cells, or endothelium, become injured by various stimuli such as hemodynamic disturbances, chemicals (e.g. from smoking) or hyperlipidaemia (e.g. increased low-density lipoprotein [LDL]). *Endothelial dysfunction, activation, and leakage*: The endothelium becomes gradually infiltrated by fatty substances, mainly LDL which transport cholesterol in the body, leading to an inflammatory response. Immune cells called monocytes are attracted and adhere to the lesion area. *Foam cell and fatty streak formation:* As monocytes mature into macrophages in the sub-endothelial space and engulf oxidised LDL, they become "foam cells". The accumulation of lipid-containing foam cells forms a fatty streak, the first visible lesion in the development of atherosclerosis. This stage is reversible.
Plaque progression	Smooth muscle cells, which form the layer beneath endothelial cells, migrate from the media (middle layer of the blood vessel) to the intima (inner layer), proliferate and increase production of extracellular matrix molecules such as collagen. Monocytes and macrophages continue to be drawn to the lesion and eventually die, forming a necrotic core of lipids under a fibrous cap made of connective tissue and smooth muscle cells.
Plaque disruption	The plaque continues to enlarge and protrude into the lumen of the blood vessel. "Stable plaques" have a thick fibrous cap and a small lipid core and are less susceptible to rupture. A thin fibrous cap and fissures can lead to a "vulnerable plaque" which may rupture and result in life-threatening thrombosis, the formation of a blood clot inside the blood vessel.

2.4 CVD PREVENTION

Following the adoption by the UN General Assembly of the Declaration addressing the prevention and control of NCDs in 2011,[17] the WHO developed a *Global NCD Action Plan* (2013-20) with a global target of reducing the risk of premature death (defined as between 30 and 70 years of age) from NCDs by a relative 25% from its 2010 level by 2025.[18] Alongside the *NCD Global Monitoring Framework* to help track the implementation of the action plan and monitor worldwide progress, global voluntary, specific targets were set that involve the following key behavioural and physiological risk factors: physical inactivity, excessive salt intake, tobacco use, excessive alcohol intake, obesity, elevated blood pressure, raised blood glucose, and diabetes mellitus.[19] As the highest proportion of deaths worldwide is attributable to CVD, targeting the major risk factors of CVD, including hypertension and diabetes mellitus, is critical to achieving this global goal.[20] As a WHO member state, Australia is committed to the global action plan and has developed its own *National Strategic Framework for Chronic Conditions* which provides high-level guidance for the planning and development of policies, strategies, actions and services for the effective prevention and management of chronic conditions. This national framework also recognises the importance of reducing health risk factors including behavioural risk factors.[21]

CVD prevention can occur both at the population and at an individual level. Population-wide strategies aim to promote healthy lifestyle behaviours in the population as a whole, including in individuals that are at low or moderate risk of developing CVD, which form the majority of the population.[22] Population-wide strategies, through policy and environmental changes, mass media campaigns or large-scale health education and promotion that can influence behaviour change, aim to reduce exposure to risk factors or increase exposure to protective factors. Some examples of the population approach include reducing the salt content of processed foods that are sold to the population, to increase tobacco taxes to reduce tobacco consumption, or to promote healthy eating through national education campaigns.[23] While the population approach aims to control the underlying causes of CVD and reduce the incidence (or rate of occurrence) of CVD, the individual approach is targeted at individuals that are identified as being at high risk for CVD, such as clinical interventions among those with hypertension or hyperlipidaemia.[24] The objective of this approach is to reduce CVD risk and levels of risk factors by preventive treatment, using pharmacological and/or non-pharmacological means. It is generally recognised that both population-wide and

individual approaches are complementary and essential in lowering the CVD risk distribution of the population.[25]

2.4.1 Risk factors for CVD

Risk reduction is central to primary prevention efforts aiming to prevent the occurrence of CVD. Risk factors are characteristics or exposures that are associated with an increased risk of developing a disease. Cardiovascular risk factors can be largely categorised as non-modifiable, such as family history and most demographic characteristics, and modifiable, such as lifestyle behaviours and metabolic risk factors.

2.4.1.1 Non-modifiable

Risk factors that cannot be modified include age, a family history of CVD, ethnicity, and gender. Generally, CVD risk increases with age and is higher in individuals with a family history of CVD in first-degree relatives, and in certain ethnic groups such as in South Asians. The risk for CVD is higher in men than in women. The difference between men and women narrows after women reach menopause and the risk for CVD can become equal after menopause.[26]

2.4.1.2 Modifiable behavioural and metabolic cardiovascular risk factors

The WHO estimates that up to 80% of premature heart disease and stroke could be prevented by a healthy lifestyle.[27] Changes in lifestyle risk factors can influence metabolic/physiologic factors such as overweight and obesity, hypertension, hyperlipidaemia, and hyperglycaemia which contribute to increasing CVD risk. The four major modifiable behavioural risk factors, common to most NCDs including CVD, are physical inactivity, an unhealthy diet, tobacco smoking, and excessive alcohol consumption.[28] Together with related metabolic/physiologic factors, these four behavioural risk factors are responsible for a large proportion of premature deaths and disabilities worldwide[29] and feature among the nine most important modifiable risk factors for acute myocardial infarction and stroke reported in the two large, international, INTERHEART and INTERSTROKE case-control studies.[30-32] In the 2016 Global Burden of Disease Study, smoking (124.1 million DALYs), high systolic blood pressure (122.2 million DALYs), alcohol intake and high fasting plasma glucose were among the top five leading risk factors for disease burden in men. In women, the leading metabolic risk factors were high systolic blood pressure (89.9 million

DALYs), high body mass index (64.8 million DALYs), and high fasting plasma glucose (63.8 million DALYs).[33]

In 2011, the leading risk factors for disease burden in Australia were tobacco smoking (9%), overweight and obesity (7%), dietary risk factors (7%), alcohol intake (5.1%), physical inactivity (5%), and high blood pressure (4.9%).[34,35] In both Australian men and women aged 45 to 64 years, a high body mass index, physical inactivity and high blood pressure featured among the top five leading risk factors.[34] In terms of CVD burden, high blood pressure (32%), physical inactivity (21%), high body mass index (21%), high cholesterol (16%), tobacco smoking (12%), low fruit (10%) and low vegetable (8.9%) consumption were all significant contributors.[34] Recent prevalence data of traditional lifestyle and metabolic factors in Australia are presented in **Table 2.3**. Overall, nine in ten Australian adults reported low vegetable consumption. Approximately half reported being physically inactive (<150 minutes in the past week) and consuming low amounts of fruit, with women being slightly more likely to be inactive than men and to consume more fruit. While a quarter of men consumed excessive amounts of alcohol and nearly a fifth were current smokers, the prevalence rates were lower in women. Over two-thirds of men and more than half of women reported being overweight/obese. Nearly two-thirds of Australian adults reported having high blood lipids. Nearly a quarter of men and more than a fifth of women reported having high blood pressure.

Table 2.3. Prevalence[a] of major lifestyle and metabolic risk factors in individuals aged 18 years and over[b], and in men and women.

	Percent		
Lifestyle/metabolic risk factor	**Men**	**Women**	**Overall**
Low vegetable consumption[c]	96.2	89.8	92.9
Physical inactivity[d]	50.6	53.7	52.2
Low fruit consumption[c]	56.0	44.6	50.2
Excessive alcohol intake[e]	25.8	9.3	17.4
Daily smoking	16.9	12.1	14.5
Overweight/obesity	70.8	56.3	63.4
Dyslipidaemia[f]	63.7	62.8	63.2
High blood pressure[g]	24.4	21.7	23.0
Impaired fasting glucose[h]	4.1	2.1	3.1

[a] Sources: ABS National Health Survey 2014-15 and AIHW analysis of unpublished ABS Australian Health Survey, 2011-12 (National Health Measures Survey Component).[36,37]

[b] The age group examined was 18-64 years for physical inactivity.

[c] According to 2013 Australian Dietary Guidelines for recommended daily serves of fruit and vegetables based on an individual's age and sex.[38]

[d] <150 minutes of physical activity in the past week.

[e] On average >2 standard drinks per day (National Health and Medical Research Council guidelines).[39]

[f] Abnormal blood lipid levels; measured and defined as having one or more of the following: total cholesterol ≥5.5 mmol/L, LDL cholesterol ≥3.5 mmol/L, triglycerides ≥2.0 mmol/L, high-density lipoprotein (HDL) cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women, taking lipid-lowering medication.

[g] Measured and defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or taking antihypertensive medication.

[h] Higher than usual blood glucose levels after fasting (6.1-6.9 mmol/L) but below diabetic levels.

Adapted from "Risk factors to health" by the AIHW, 2017.[40]

i. Physical inactivity

The term "physically inactive" describes people that do not engage in sufficient levels of physical activity to meet physical activity guidelines. For optimal health benefits, both the WHO and Australian guidelines recommend at least 150 minutes of moderate intensity physical activity, 75 minutes of vigorous intensity physical activity, or an equivalent combination of both, per week.[41,42] Compared to individuals that report no leisure time physical activity, those that meet or exceed the recommended amounts of 150 minutes/week of moderate intensity or 75 minutes/week of vigorous intensity physical activity have a 31% to 39% lower risk of mortality.[43] Physical inactivity contributes substantially to deaths and disability attributed to CVD and other NCDs. Physical inactivity was ranked as the fourth leading cause of death in 2009, accounting for 6% of deaths and 2.1% of total DALYs (32.1 million DALYs) worldwide.[44] Physical inactivity contributed an estimated 13.4 million DALYs in 2013 based on the following five NCDs: CHD (5 million DALYS), stroke (4.5 million DALYs), type 2 diabetes (2.3 million DALYs), breast cancer

(0.9 million DALYs), and colon cancer (0.7 million DALYs).[45] In Australia, physical inactivity accounted for 2.6% of total DALYs (116,676 DALYs) in 2011, with the following proportions attributable to each linked disease due to physical inactivity: 11% for CHD, 10% for stroke, 19% for diabetes, 16% for bowel cancer, 16% for uterine cancer, 11% for breast cancer, and 14% for dementia.[46] Based on self-reported data from Australian National Health Surveys, the high prevalence of physical inactivity has remained unchanged between 1989 (38.7%) and 2011 (37.3%), with observed prevalence levels over time tending to decrease in men and increase in women.[47]

Regular physical activity can help lower the risk of CHD, stroke, and associated conditions such as overweight/obesity, type 2 diabetes, and hypertension. Physical activity increases energy expenditure, promotes weight loss/maintenance, lowers blood pressure, and improves glucose, insulin and lipid metabolism, contributing to overall cardiovascular health.[48] In a 2010 meta-analysis of prospective cohort studies, high levels of leisure time physical activity were associated with a 20% to 30% lower risk of developing CHD and stroke in both men and women, compared to low levels of physical activity.[49] The benefits of physical activity extend to other diseases and it is associated with lower levels of stress, depression, and anxiety, which can contribute to cardiovascular health as well as psychosocial wellbeing.[50]

ii. Fruit and vegetable consumption

Whilst they vary by country, dietary guidelines generally advocate consuming an adequate amount of fruit and vegetables as part of a healthy diet. The WHO recommends consuming a daily minimum of 400g or the equivalent of five portions of fruit and vegetables for the prevention of chronic diseases.[51] The Australian dietary guidelines recommend eating a minimum of two serves of fruit and five serves of vegetables per day.[38] In 2014-15, about half of Australians reported consuming the recommended daily intake for fruit, 7% met the guidelines for vegetable intake, and only 5.1% (7.5% of women, 2.7% of men) met both fruit and vegetable guidelines.[52] Between 2001-15, the proportion of Australians not meeting the recommended daily amounts of fruit and vegetables increased by approximately 3% for fruit (2.6% in women, 3.2% in men) and 7% (8.3% in men, 5.6% in women) for vegetables.[52]

In the Global Burden of Disease Study 2010, dietary risk factors ranked among the leading risk factors for global disease burden with diets low in fruit being the largest dietary contributor

(4.9 million deaths, 4.2% of total DALYs), followed by diets high in sodium (4 million deaths, 2.5% of total DALYs).[53] Diets low in vegetables also contributed significantly to global disease burden (1.8 million deaths, 1.5% of total DALYs).[53] In Australia, insufficient fruit and vegetable consumption were responsible for 2.0% and 1.4% of total DALYs respectively, in 2011.[34] Several meta-analyses have provided evidence that fruit and vegetable consumption are protective against the risk of CHD,[54,55] stroke,[56] cardiovascular and all-cause mortality.[57,58] A 200 g/day increment in the separate or combined consumption of fruit and vegetables has been associated with a risk reduction of 8-16% for CHD, 13-18% for stroke, 8-13% for CVD, and 10-15% for all-cause mortality.[53] In another meta-analysis, each additional daily serving was associated with a 4% reduction for fruit and vegetables combined, 5% for fruit consumption, and 4% for vegetable consumption in the risk of CVD mortality.[58]

Fruit and vegetables are rich in multiple nutrients such as dietary fibre, antioxidants, potassium, and phytochemicals that can act synergistically via different mechanisms to help lower the risk of CVD and premature death. Mechanisms include reducing oxidative stress, blood pressure, systemic inflammation, and improving lipoprotein profiles and insulin sensitivity.[59]

iii. Smoking

Smoking cessation is recommended to reduce the health risks associated with tobacco smoking. In 2015, tobacco smoking was the second global leading risk factor for premature mortality and disability, and was responsible for 11.5% of deaths and 148.6 million DALYs worldwide.[60] CVD (41.2%) was the leading cause of age-standardised DALYs attributable to smoking.[60] In 2011, smoking was responsible for the largest proportion (9%) of burden of disease in Australia.[34] However, rates of tobacco smoking have declined substantially in Australia over the past two decades. The proportion of daily smokers decreased from 22.4% in 2001 to 14.5% in 2014-15.[36]

Smoking at any level increases CVD risk. In addition to being a strong independent risk factor for CVD, smoking has a multiplicative effect on disease risk when combined with other risk factors.[61] Smoking can contribute to vascular dysfunction including blood vessel wall damage, stiffness, lower coronary blood flow and oxygen level, and higher blood pressure. In addition, smoking increases inflammation, oxidative stress, thrombosis and atherosclerotic plaque formation which can lead to cardiovascular events.[62] There is solid evidence that smoking

cessation can reverse the physiological damage caused by smoking, have immediate and long-term beneficial health effects, and reduce mortality from CVD.[62,63]

Exposure to smoking or second-hand smoking is also an important preventable cause of disease, disability, and death. In 2004, the WHO estimated that approximately 1% of all global deaths and 0.7% of global DALYs were due to second-hand smoking.[64] Of the 603,000 estimated yearly deaths (47% in women, 28% in children, 26% in men) caused by second-hand smoking, nearly two-thirds resulted in deaths from CHD. CHD also accounted for a large proportion of estimated DALYs.[64] In Australia, the only data that could be found on second-hand smoking dated from 2004-05. During that period, second-hand smoking was responsible for an estimated 141 deaths, 90% of which were from CHD. These figures were likely underestimated as several diseases not known to be associated with second-hand smoking at the time were not included and conservative methods were used to estimate CHD deaths.[65] Australia has developed a National Tobacco Strategy and adopted several smoke-free laws.[66] The WHO has created a Framework Convention on Tobacco Control to promote tobacco-smoke-free environments.[67]

iv. Alcohol

While guidelines worldwide vary as to what constitutes safe levels of alcohol consumption and the definition of a standard drink, the current Australian guidelines recommend no more than two standard drinks (one standard drink contains 10 g of alcohol) per day to reduce health risks associated with alcohol consumption.[39] In middle-aged populations, alcohol consumption may have a U-shaped or J-shaped relationship with the risk of CHD and stroke, where abstention and higher levels of consumption may be linked with increased risk compared with low to moderate drinkers.[68,69] Excessive alcohol consumption and episodes of heavy drinking have been linked with increased mortality and cardiovascular risk.[70,71] Alcohol consumption ranked as the seventh leading global risk factor for deaths (2.2% of age-standardised deaths in women and 6.8% in men) and disability (1.2% of DALYs in women and 6% in men).[72] In Australia, alcohol was the eighth leading risk factor for burden of disease, illness and injury, accounting for 2.1% and 2.8% of total deaths and DALYs respectively in 2010.[73] Between 2004-05 and 2014-15, the rates of excessive alcohol drinking decreased in Australia, relatively more in men (from 32% to 26%) than in women (from 12% to 9.2%)[40]

While alcohol intake may have beneficial effects on specific lipids such as increasing anti-atherogenic HDL cholesterol levels and on fibrinolytic activity, it can increase blood pressure which can lead to adverse cardiovascular health effects (this mechanism is further described in section *vi*).[70] Given that alcohol consumption is an important risk factor for global disease burden, strategies at the population level are being put in place to reduce the harmful consumption of alcohol.

v. Overweight and obesity

WHO defines overweight as a body mass index ≥25 kg/m^2 and obesity as a body mass index≥ 30 kg/m^2.[74] Australia uses the same classification to measure overweight and obesity at the population level. Overweight and obesity is an important risk factor for CVD, type 2 diabetes, and hypertension. In 2015, a high body mass index accounted for 7.1% of total deaths (4 million deaths) and 4.9% of total DALYs (120 million DALYs) worldwide.[75] CVD was the leading cause of body mass index-related deaths (2.7 million deaths) and DALYs (66.3 million DALYs), followed by diabetes.[75] In 2011, overweight and obesity was the second leading risk factor for disease burden in Australia, with a higher burden in men (7.3% of total DALYs) than in women (6.6%), and 84% of the burden occurring in people aged 45 years and over.[37] CVD (38%) followed by diabetes (17%) accounted for most of the burden due to overweight and obesity. Men had a higher attributable burden due to CVD (50%) than women (34%), which was mainly due to a greater CHD burden in men.[37] The prevalence of overweight and obesity has increased by 6% between 1995 and 2015, mainly due to a 9% rise in the prevalence of obesity.[76]

Overweight and obesity can lead to high blood pressure, high blood lipids and glucose, by adversely affecting adipose tissue adipokine secretion, inflammatory pathways, and cardiovascular structure, function and hemodynamics.[77] Adopting healthy lifestyle behaviours including eating a healthy diet and engaging in adequate levels of physical activity can help manage overweight and obesity.

While obesity appears to be detrimental for cardiovascular health at the population level, an "obesity paradox" has emerged in recent years whereby obesity appears to confer a better prognosis in overweight and mildly obese individuals with established CVD relative to normal weight counterparts.[77,78] The obesity paradox has been described in the context of different types of CVD including CHD, myocardial infarction, hypertension, heart failure, atrial fibrillation and

in cardiac surgery patients. However, the obesity paradox is still the subject of much debate as is its potential mechanism. For example, most studies use body mass index which does not measure regional adiposity and lean muscle mass which may have different effects on survival.[77] Several other methodological concerns in relation to previous studies reporting an obesity paradox have been highlighted, including confounding by smoking, reverse causation, and effect modification by age.[79] Cardiorespiratory fitness may also be an important factor to consider in examining associations between overweight and obesity and mortality as a high cardiorespiratory fitness may offer protective effects to overweight and obese individuals.[79] A recent paper has also questioned the obesity paradox by showing that greater longevity in individuals that are overweight or obese could be explained by an earlier diagnosis of CVD compared with individuals with a healthy BMI.[80]

vi. Hypertension

Hypertension, defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or both, is a major risk factor for CVD. Modifiable risk factors for hypertension include overweight and obesity, insufficient physical activity, high salt intake and excessive alcohol intake.[81] In 2015, high systolic blood pressure was among the top three global leading risk factors for global burden of disease, in both men and women, contributing to 8.9% of global DALYs.[33] A systolic blood pressure of 140 mmHg or higher has been associated with 15% of deaths worldwide, with 41% of blood pressure-related deaths due to CVD.[82] In Australia, high blood pressure was ranked as the fifth risk factor accounting for the most overall burden in 2011. High blood pressure caused the most CVD burden (32%), especially in relation to stroke and CHD.[34] Between 1980 and 2011-12, the prevalence of high blood pressure measured in adults aged 25 to 64 years decreased substantially, by approximately 25% in men and 15% in women.[83]

Several potential mechanisms link hypertension to CVD. Hypertension can damage blood vessels, cause endothelial dysfunction, accelerate the atherosclerotic process, and lead to unstable plaques and acute coronary events. A common complication of hypertension is developing left ventricular hypertrophy which can lead to myocardial infarction.[84]

vii. Hyperglycaemia and type 2 diabetes

Elevated blood glucose levels or hyperglycaemia, even at levels below those indicative of diabetes, increases the risk for type 2 diabetes, cardiovascular mortality and all-cause mortality. In

the Global Burden of Disease Study 2016, high fasting blood glucose levels was the fifth leading risk factor worldwide for disease burden.[33] In the large INTERHEART study, glycated haemoglobin (HbA1c), which is a measure of the average blood glucose levels in the previous 6 to 8 weeks, was an independent predictor of myocardial infarction in both individuals with and without diabetes, and in both men and women, after accounting for nine other established risk factors including diabetes.[85]

Type 2 diabetes is diagnosed in a clinically relevant context, with indicators including fasting glucose levels ≥7 mmol/L, 2 hour plasma glucose levels ≥11.1 mmol/L on the 75 g oral glucose tolerance test, and an HbA1c level ≥ 6.5%. Type 2 diabetes itself is a major risk factor for CVD because of its microvascular and macrovascular effects. Lifestyle risk factors for type 2 diabetes include a poor diet, low physical activity, high sedentary behaviour, smoking.[86] While men with type 2 diabetes have two to three times the risk of developing CVD, women with diabetes have a three to four times higher risk than non-diabetic counterparts.[87] In 2012, type 2 diabetes was the eighth leading cause of death worldwide, and the fifth in women.[88] Type 2 diabetes was the sixth leading cause of disability in the world in 2015.[89] In Australia, type 2 diabetes contributed to 10% of deaths in 2015, with mortality rates nearly two times higher in men than women.[90] Close to two-thirds of deaths in Australians that have diabetes are due to CVD.[91] Between 1989-90 and 2014-15, the prevalence of self-reported diabetes in Australia has tripled from 1.5% to 4.7%.[92]

Both insulin resistance and impaired pancreatic insulin secretion have been implicated in the pathophysiological mechanism leading to high blood glucose levels in the fasting and postprandial states in pre-diabetic individuals.[93] Hyperglycaemia and fluctuations in blood glucose levels can generate oxidative stress, inflammatory responses, insulin resistance, pancreatic β cell dysfunction, and endothelial dysfunction which can subsequently lead to microvascular and macrovascular complications.[94] Type 2 diabetes is also commonly associated with a cluster of cardiovascular risk factors which contribute through various mechanisms to CVD.[95] Making healthy lifestyle changes is important for glycaemic control and type 2 diabetes prevention.

viii. Hyperlipidaemia

Hyperlipidaemia is characterised by abnormally high levels of lipids in the blood such as triglycerides levels ≥2.0 mmol/L, total cholesterol levels ≥5.5 mmol/L or LDL cholesterol ≥3.5 mmol/L. Hyperlipidaemia is an established risk factor for CVD. Several meta-analyses have

shown that both total and LDL cholesterol are positively associated with CVD risk, while HDL cholesterol is inversely related to CVD risk.[96-98] In the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, high total cholesterol was the eighth leading contributor to global disease burden (93.8 million DALYs).[33] According to the WHO, high cholesterol accounts for a third of global CHD deaths.[99] In Australia, high cholesterol was responsible for 2.4% of total DALYs, 28% of DALYs attributable to CHD, and 7.2% of DALYS due to stroke in 2011.[34] Between 2010 and 2014, the proportion of adults aged 30 to 65 years with self-reported medically diagnosed high cholesterol (33%) remained stable, with rates slightly higher in men (37%) than in women (29%).[83]

Hyperlipidaemia can lead to endothelial dysfunction and initiate the atherosclerotic process described earlier in section 2.3. Adopting a diet low in saturated and trans fats, engaging in physical activity, not smoking, not drinking alcohol excessively and weight loss can help lower prevent hyperlipidaemia.[100]

2.4.1.3 Novel approaches to lifestyle risk factors

In addition to known modifiable risk factors described in the previous section, research about novel approaches to lifestyle risk factors and emerging knowledge about lesser known risk factors could be valuable to consider in prevention strategies for CVD.

i. Multiple risk factors

For decades, lifestyle risk factors have often been studied as single risk behaviours in relation to CVD outcomes. There has been limited research on the clustering of different lifestyle risk factors and the interactions between risk factors. Yet, many lifestyle behaviours tend to cluster together within individuals and may have synergistic effects on disease risk.[101] There is growing evidence showing the importance of considering the combined influence of lifestyle risk factors, including specific risk factor combinations, on multiple disease outcomes. Several studies have examined risk factors jointly and reported the benefits of adopting healthy lifestyle behaviours for better health outcomes in relation to CHD,[102] myocardial infarction,[103] diabetes,[104] cardiovascular mortality[105] and all-cause mortality.[106] There was an eighth-fold higher risk in cardiovascular mortality among middle-aged women with five lifestyle risk factors (low diet quality, low physical activity, smoking, heavy alcohol consumption, overweight) compared with none.[105] A recent meta-analysis has reported a 66% lower risk in all-cause mortality in individuals that engaged in at least four healthy lifestyle behaviours compared to individuals with an unhealthy lifestyle (unhealthy

diet, no physical activity, smoking, no or excessive alcohol consumption, obese).[106] Exploring the combined influence of lifestyle risk factors rather than in isolation can help inform and develop more effective public health prevention strategies.

Two-thirds of Australian adults had three or more risk factors in 2011-12.[107] The top three most common combinations with two risk factors were: consuming insufficient amounts of fruit and vegetables and being overweight/obese (55%), being overweight/obese and having dyslipidaemia (34%) and being physically inactive/insufficiently active and overweight/obese (33%). The top three most common combinations with three risk factors were: consuming insufficient amounts of fruit and vegetables, being physically inactive/insufficiently active and being overweight/obese (31%); being physically inactive/insufficiently active, being overweight/obese and having dyslipidaemia (19%); and consuming insufficient amounts of fruit and vegetables, being physically inactive/insufficiently active and having uncontrolled high blood pressure (11%).

Based on national data from 2007-08, the distribution of numbers of lifestyle/behavioural risk factors was generally similar for men and women as were the types of risk factor combinations in the top 10 most common combinations.[108] Consuming insufficient amounts of fruit and vegetables and being physically inactive/insufficiently active were most often present among the 10 most common combinations overall and within most age groups.[108]

ii. Emerging/lesser known lifestyle risk factors

Recently identified lifestyle risk factors/behaviours that may be linked with CVD and that are examined in this thesis include raw vegetable consumption, sedentary behaviour, psychological distress, and breastfeeding. These less well established lifestyle risk factors are briefly described in this section and their importance is further explored in studies presented in **Chapters 3 to 7**.

Promoting vegetable consumption for overall health is important for Australian adults as the large majority (93%) does not consume vegetables in recommended amounts.[52] A few studies have reported that the consumption of raw vegetables compared to that of cooked vegetables may offer stronger protective effects for mortality and CVD.[109-111] Cooking can change the nutritional properties of vegetables and their subsequent physiological effect on health. However, the number of studies examining the differential effects of raw versus cooked vegetables has been limited and further research is required.

In Australia, the guidelines for sedentary behaviour recommend lowering the amount of time spent in prolonged sitting and breaking up long periods of sitting.[41] Evidence is accumulating that sedentary behaviour may be an important lifestyle risk factor to consider in relation to CVD outcomes. Sedentary behaviour (including daily sitting and screen time) is thought to contribute to poor health and CVD outcomes, possibly partly independent of moderate-to-vigorous physical activity.[112,113] In Australia, 42% of men and 36% of women reported sitting or lying down for leisure, transport or work in 2011-12.[114] The mechanism mediating the association between sedentary behaviour and CVD remains unclear but may involve hemodynamic, inflammatory and metabolic changes.[115]

Poor mental health including psychological distress is also emerging as a risk factor that has been associated with CVD in several meta-analyses.[116-119] Psychological distress, a general measure of mental health and wellbeing, is strongly correlated with diagnosis of anxiety and depression,[120] which are both associated with an increased risk for CVD.[116,117,119] The mechanisms linking psychological distress to CVD remain to be elucidated. However, activation of the hypothalamic-pituitary-adrenal axis, altered autonomic nervous system and inflammatory processes may be involved.[121] It has also been reported that behavioural risk factors may serve as intermediary risk factors in the association between psychological distress and CVD.[122] In 2014-15, one in nine Australian adults reported high or very high levels of psychological distress, with higher rates reported in women (13.5%) than in men (9.9%).[36]

Evidence is also growing about a potential link between breastfeeding, a behaviour unique to women, and maternal risk of CVD later in life.[123] Breastfeeding has been associated with a lower risk of hypertension,[124] type 2 diabetes,[125] as well as CVD incidence[126] and mortality.[127] While breastfeeding may help to reverse the adverse metabolic effects of pregnancy,[128] the mechanism for a longer-term association with CVD is currently unclear. Further longitudinal studies are needed to explore the potential role of breastfeeding as a modifiable risk factor for CVD. Infant feeding guidelines in Australia currently recommend exclusively breastfeeding infants until approximately six months of age and then continued breastfeeding combined with solid food until 12 months of age.[129]

Examining the numerous other emerging cardiovascular risk factors is beyond the scope of this thesis. However, the role of inflammation and associated markers in relation to cardiovascular

risk should be briefly mentioned. Chronic low-grade inflammation plays a key role in the atherosclerotic process. Among novel and emerging inflammatory markers that have been identified, C-reactive protein (CRP) has received considerable attention. It is associated with increased cardiovascular risk and can predict future cardiovascular events.[130] Given that several behavioural and metabolic risk factors may influence the inflammatory process, adopting a healthy lifestyle is of central importance.

2.4.2 Importance of CVD prevention in the middle-aged population

In 2013, NCDs were responsible for the majority of deaths among individuals aged 45 years and over. The largest proportion of NCD-related deaths was attributed to CVD in adults over 40 years, with this proportion progressively increasing during middle age years (typically between 45 to 65 years of age[131]) and beyond.[132] In 2015, 29% and 19% of NCD deaths in Australian men and women, respectively, occurred prematurely.[133] In 2011-13, CHD was the leading cause of premature death in Australia, including in adults aged 45 years and over, and in men. In women, CHD ranked as the third leading cause of premature death.[8]

Risk factors during middle age years can determine the risk of CVD at older ages. Indeed, lower levels of behavioural and physiological risk factors in middle-aged adults have been associated with markedly lower risks for CVD several decades later, and longer survival.[134,135] With a growing and ageing population, identifying CVD prevention strategies that are informed by research evidence and which focus on modification of risk factors in the middle-age population should be a public health priority.

The prevalence of cardiovascular risk factors in Australian men and women aged 45 years and over is presented in **Table 2.4**. With the exception of physical inactivity which was more prevalent in women than men, all other risk factors were more prevalent in men.

Table 2.4. Prevalence[a] of traditional lifestyle and metabolic risk factors in individuals aged 45 years and over, and in men and women.

	Percent		
Lifestyle/metabolic risk factor	**Men**	**Women**	**Overall**
Physical inactivity[b]	68.3	73.3	70.7
Low fruit consumption[c]	52.7	39.4	45.7
Low vegetable consumption[c]	96.8	88.7	91.6
Current smoker	15.6	11.7	13.5
Excessive alcohol intake[d]	40.3	20.5	31.6
Overweight/obesity	79.5	65.8	72.4
High blood pressure[e]	36.4	33.2	34.6
Diabetes[f]	-	-	8.7
High total cholesterol[f,g]	-	-	41.4

[a] Calculated based on data from the ABS National Health Survey 2014-15 (for lifestyle risk factors, overweight/obesity and high blood pressure) and Australian Health Survey 2011-12 (for diabetes and high total cholesterol).[36,37]

[b] <150 minutes in the past week.[41]

[c] According to 2013 Australian Dietary Guidelines for recommended daily serves of fruit and vegetables based on an individual's age and sex.[38]

[d] On average >2 standard drinks per day.[39]

[e] ≥140/90 mmHg.

[f] The prevalence rates for men and women aged ≥45 years could not be calculated from available data for diabetes and total cholesterol.

[g] ≥5.5 mmol/L.

2.4.3 Importance of CVD prevention with a gender focus

CVD is the leading cause of death worldwide not only in men but also in women, contributing nearly equally to global death rates in both sexes in 2015.[136] Although historically thought to be a "man's disease", men generally develop CVD at a younger age while women tend to develop CVD as they get older. There are well recognised differences between women and men in the epidemiology, pathophysiology, risk factors, treatment, and outcomes of CVD (**Table**

2.5).[137-150] In addition, women have unique reproductive risk factors to consider[140,143,145] (**Table 2.6**).

Table 2.5. Gender differences in CVD[a].

Parameter	Difference in women (relative to men)
Lifestyle risk factors	
Physical inactivity	Higher prevalence[131,152]
Unhealthy diet	Lower prevalence[141]
Smoking	Lower prevalence[140] Confers a higher risk of CVD (e.g. CHD)[139,140,150]
High alcohol intake	Lower prevalence[138,148]
Sedentary behaviour	Higher prevalence[139]
Depression	Higher prevalence[140,146] Confers a higher risk of CVD mortality[140,143,146,150]
Physiological risk factors	
Obesity	Different prevalence based on country[142] Confers a higher risk of CVD[139]
Hypertension	Higher prevalence at older age[139,145] Less controlled[139] Confers a higher risk of CVD[145,149]
Type 2 diabetes	Higher prevalence Confers a more adverse cardiovascular risk profile[147] Confers a higher risk of CVD (e.g. CHD, heart failure)[137,140,145,150]
Dyslipidaemia	Specific lipoproteins seem to be more important risk factors in women (e.g. low HDL cholesterol and high triglycerides)[137]
Risk awareness	More likely to underestimate the impact of CVD on their health[137] Less likely aware of risk factors for CVD
Age of CVD onset	Later onset (e.g. CHD typically occurs 7-10 years later)[137,144,145]
Disease pathophysiology	Lower atheroma volume, smaller vessel size, less plaque rupture, remodelling differences, functional differences in smooth muscle cells[137,145]
Types of CVD[b]	

CHD	Less likely to have as a first event[144]
Cerebrovascular disease	More likely to have as a first event[144] Worse stroke severity and poorer functional outcomes following stroke
CVD symptoms	More likely to present with atypical symptoms (e.g. abdominal pain, jaw pain, nausea)[137] CHD symptoms more complex and multifactorial
CVD diagnosis	Less likely to be diagnosed given the same symptoms, and receive treatment Less likely to receive electrocardiography upon presentation at the emergency department[137] Less often referred for diagnostic tests[137] Non-invasive testing predicts CVD less accurately[137] Higher incidence of silent MI[137]
CVD treatment	More likely to delay seeking treatment[137] Differences in effectiveness, interactions and side effects[145] Less invasive interventions[137] Less likely to receive secondary prevention medication[137] Less referrals and lower participation rates in cardiac rehabilitation programs[137] Less likely to adopt healthy lifestyle behaviours
CVD outcome	More likely to have adverse outcomes[137] Higher mortality rates following MI[137]

Abbreviations: CHD=coronary heart disease, CVD=cardiovascular disease, ECG=electrocardiography, HDL=high-density lipoprotein, MI=myocardial infarction.

[a] The information presented on this table is adapted from the following references 137 to 150.

[b] Relevant to this thesis are presented in this table.

Table 2.6. Women-specific risk factors in CVD.

Pregnancy-related disorders	Gestational hypertension and pre-eclampsia are associated with a higher risk of hypertension and CVD later in life[140,143,145] Gestational diabetes confers a higher risk of type 2 diabetes and CVD later in life[140,143,145]

Hormonal dysfunction pre-menopause	Confers a higher risk of CVD[145]
Menarche	Early menarche confers a higher risk of CVD[140]
Menopause	Early onset menopause (before age 45) is associated with higher risk CVD and CVD mortality[140] The increased CVD risk seen with menopause at usual age may be more age-related rather than menopause-related[140]

Abbreviations: CVD=cardiovascular disease.

While there has been both a global and Australian impetus to increase awareness about the importance of CVD as a health issue in women and to highlight it both as a public health and research priority, CVD receives insufficient prevention efforts, is underdiagnosed, undertreated, and under researched in women. There is an underrepresentation of women in research as well as a paucity of data that explores potential gender differences in CVD prevention based on lifestyle behaviour modification.[151152] Both national and international health bodies have urgently called for more gender-specific research to gain a better understanding of potential gender differences in CVD and to inform more effective prevention strategies in both women and men.[145,151,153,154]

The following five chapters present mostly published findings from prospective studies carried out as the central work in this thesis, examining associations among innovative cardiovascular risk factors in a large cohort of middle-aged and older Australian men and women. The innovative aspect of this thesis resides in the: 1) cardiovascular risk factors considered, including recently identified ones such as raw vegetable consumption, sedentary behaviour and poor mental health; 2) methodological approach which involves comparing the influence of individual versus a combination of lifestyle risk factors; 3) gender-based approach to explore potential gender differences and cardiovascular risks of behaviours specific to women, mainly breastfeeding.

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CHAPTER THREE:
Fruit and vegetable consumption and all-cause mortality: Evidence from a large Australian cohort study

3.1 PREFACE TO THE CHAPTER

This chapter presents findings from a peer-reviewed paper that examined the longitudinal association between fruit and vegetable consumption, considered separate and combined, and all-cause mortality in the 45 and Up Study cohort. In addition, the lesser known influence of consuming raw versus cooked vegetables on all-cause mortality was examined. We had originally intended to examine the association between fruit and vegetable consumption and CVD outcomes. Unfortunately, at the time of analysis, cardiovascular outcomes were not available for this cohort and hence, we could not include these in our paper. However, in a recent meta-analysis based on 16 longitudinal studies, most of the inverse association between fruit and vegetable consumption and all-cause mortality was accounted for by mortality from CVD.[1]

This chapter, consisting of the published paper, addresses specific aims #1 and #5 of this thesis as described in Chapter 1. Dissemination of this research and author contributions for this paper are described below.

3.2 RESEARCH DISSEMINATION

The research presented in this chapter has been disseminated as follows:

Published peer-reviewed paper

Nguyen B, Bauman A, Gale J, Banks E, Kritharides L, Ding D. Fruit and vegetable consumption and all-cause mortality: evidence from a large Australian cohort study. *International Journal of Behavioral Nutrition and Physical Activity* 2016; 13: 9. Available from: http://doi.org/10.1186/s12966-016-0334-5

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Nguyen B, Bauman A, Gale J, Banks E, Kritharides J, Ding D. Fruit and vegetable consumption and all-cause mortality: Evidence from a large Australian cohort study. *Health Data Linkage Showcase, Menzies Centre for Health Policy*, Sydney, Australia, 2017. [Oral presentation]

3.3 AUTHOR ATTRIBUTION STATEMENT

I, Binh Nguyen, was responsible for designing the study, interpreting data, writing drafts of the manuscript, submitting the manuscript, responding to reviewers' comments, and coordinating submission and publication of the manuscript.

My co-authors, A. Bauman, J. Gale and D. Ding, helped to design the study. J. Gale conducted the statistical analyses. A. Bauman and D. Ding helped draft the manuscript. A. Bauman, J. Gale and D. Ding helped to interpret data and to revise the manuscript critically for important intellectual content.

All authors have read and approved the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.

Signature:

Dr. Ding (Melody) Ding

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RESEARCH Open Access

Fruit and vegetable consumption and all-cause mortality: evidence from a large Australian cohort study

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Abstract

Background: There is growing evidence for a relationship between fruit and vegetable consumption and all-cause mortality. Few studies, however, specifically explored consuming raw versus cooked vegetables in relation to health and mortality outcomes. The purpose of this study was to examine the relation of all-cause mortality with: a) fruit and vegetable consumption, either combined or separately; b) the consumption of raw versus cooked vegetables in a large cohort of Australian middle-aged and older adults.

Methods: The sample included 150,969 adults aged 45 years and over from the 45 and Up Study, a prospective cohort study conducted in New South Wales, Australia. Self-reported baseline questionnaire data (2006–09) were linked to mortality data up to June 2014. Fruit and vegetable consumption was assessed by validated short questions. Crude and adjusted hazard ratios were calculated using Cox proportional hazard models. Covariates included socio-demographic characteristics, health-related and dietary variables.

Results: During a mean follow-up of 6.2 years, 6038 (4 %) participants died from all causes. In the fully adjusted models, increasing consumption of fruit and vegetables combined was associated with reductions in all-cause mortality, with the highest risk reduction seen up to 7 serves/day or more of fruit and vegetables (*P* for trend = 0.002, hazard ratio for highest versus lowest consumption quartile: 0.90; 95 % confidence interval: 0.84, 0.97). Separate consumption of fruit and vegetables, as well as consumption of raw or cooked vegetables, were associated with a reduced risk of all-cause mortality in the crude and minimally adjusted models (all *P* for trend <0.05). With the exception of raw vegetables, these associations remained significant in the fully adjusted models (all *P* for trend <0.05). Age and sex were significant effect modifiers of the association between fruit and vegetable consumption and all-cause mortality.

Conclusions: Fruit and vegetable consumption were inversely related to all-cause mortality in this large Australian cohort. Further studies examining the effects of raw versus cooked vegetables are needed.

Keywords: Fruit, Vegetables, Mortality, Prospective studies

Background

High consumption of fruit and vegetables as part of a healthy diet is advocated for the prevention of chronic diseases, such as coronary heart disease, stroke, and some cancers [1]. Although dietary recommendations vary between countries, most are in line with the World Health Organization's recommendation to consume a daily minimum of 400 g of fruit and vegetables, or the equivalent of five portions of fruit and vegetables per day [1–3]. Recently, a comparative risk assessment of global burden of disease identified diets low in fruit to be among the five leading risk factors worldwide [4]. Previous meta-analyses have provided evidence for the protective effects of fruit and vegetables against risk of coronary heart disease [5, 6] and stroke [7]. A recent meta-analysis has shown that the consumption of fruit and vegetables, either separately or combined, was inversely associated with a lower risk of all-cause and cardiovascular mortality [8]. The relationship with cancer mortality is less clear [8, 9], and may be specific to the

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kinds of fruit and vegetable consumed and types of cancers [10]. With cardiovascular disease and cancer being the primary causes of death in developed countries [11], further investigation of the protective effects of fruit and vegetables can contribute to the evidence base for public health recommendations.

To date, there has been limited research on fruit and vegetable consumption and mortality risk in Australia. Previous prospective cohort studies have been conducted in the United States, Europe and Asia [5–8]. In addition, few cohort studies have investigated the consumption of raw versus cooked vegetables in relation to mortality risk or disease incidence [9, 12]. Cooking can modify the nutritional properties of vegetables thereby influencing their potential effects on health [13]. In the large European Prospective Investigation into Cancer and Nutrition cohort, stronger inverse associations were observed for raw vegetables than for cooked vegetables with all-cause, cardiovascular and cancer mortality [9]. However, both raw and processed fruit and vegetables were not significantly related to cardiovascular disease incidence in a Dutch population-based cohort [12]. A review by Link and Potter [13] including both case–control and cohort studies showed that the consumption of raw vegetables was more strongly related to specific types of cancer than that of cooked vegetables. Although results from these observational studies tend to suggest that the associations with raw vegetables may be stronger than with cooked vegetables [9, 13], this has not been firmly established.

The aims of this paper are to examine the relation of all cause-mortality with: a) individual and combined fruit and vegetable consumption; b) the consumption of raw versus cooked vegetables, in a large Australian cohort aged 45 years and over. Findings from the current study could inform public health recommendations on fruit and vegetable consumption.

Methods

Study population

The Sax's Institute's 45 and Up Study is the largest prospective cohort study into healthy ageing in the Southern Hemisphere [14]. The cohort comprises 267,153 men and women aged 45 years and over residing in the state of New South Wales (NSW), Australia at baseline, and represents around 10 % of the NSW population aged 45 years and over. From January 2006 to December 2008, potential participants were randomly sampled from the database of Medicare Australia, the national health insurance provider and were sent an invitation to take part. The database includes Australian citizens, permanent residents, and some temporary residents and refugees. Interested participants joined the study by completing a mailed questionnaire and a consent form for follow-up which included linkage of questionnaire data to population health databases. The study methods have been described in detail elsewhere [14] and the baseline questionnaire is available at http://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/. The 45 and Up Study received ethics approval from the University of NSW Human Research Ethics Committee. Approval to use data from the 45 and Up Study for this paper was obtained from the NSW Population and Health Services Ethics Committee. Participants who had reported on the baseline questionnaire that they had a history of cancer (defined as a self-reported history of cancer other than non-melanoma skin cancer: $n = 22{,}900$) and/or cardiovascular disease (defined as a self-reported history of heart disease, stroke or blood clot: $n = 46{,}120$) were excluded from the analysis. Of the remaining 203,590 participants who did not report a history of cancer and/or cardiovascular disease, 52,621 had missing data for the covariates of interest to this study and were further excluded from the analysis. The final analytic sample included 150,969 participants (83,329 women and 67,640 men).

Measurement

Exposure

Self-reported baseline questionnaire data include information on socio-demographic and lifestyle factors, height and body weight, medical and surgical history, and physical functioning. Participants were asked a few dietary questions based on short validated dietary questions commonly used in health monitoring and surveillance [15]. Usual fruit consumption was assessed by asking participants: "About how many serves of fruit do you usually have each day?" with one serve of fruit corresponding to one medium piece or two small pieces of fresh fruit, or one cup of diced or canned fruit pieces. Vegetable consumption was determined from the following question: "About how many serves of vegetables do you usually eat each day?" Participants were asked to report consumption of raw and cooked vegetables separately. One serve of vegetables was defined as half a cup of cooked vegetables (including potatoes) or one cup of raw vegetables (e.g. salad). For each of these two questions, participants also had the option to answer that they did not eat fruit or vegetables, which were subsequently coded as zero serve.

Outcome

All-cause mortality was ascertained from the NSW Registry of Births, Deaths, and Marriages from February 1, 2006 to June 15, 2014. The mortality data were linked to the 45 and Up Study baseline data by the Centre for Health Record Linkage (CHeReL, NSW, Australia) using probabilistic record linkage methods and a commercially available software (Choice-Maker, ChoiceMaker Technologies Inc.).

Covariates

The following baseline self-reported variables were included as covariates: age, sex, highest educational qualification (none, school certificate, higher school certificate, trade/certificate/diploma, university degree or higher), marital status (single, widowed, divorced/separated, or married/de facto), residential remoteness (major city, regional area, or remote area), socio-economic status (quintiles based on Socio-Economic Indexes For Area - Index of Relative Socio-Economic Disadvantage [16]), smoking status (never, past, or current), hours of sleep, physical activity (assessed using validated questions from the Active Australia Survey [17]; categorised as <150, 150–300, ≥300 min per week), multi-vitamin intake (for most of the last four weeks), processed meat intake (times per week), general health (self-rated as excellent, very good, good, fair or poor), previous physician diagnosis of diabetes (yes or no) and body mass index (derived from self-reported height and weight; categorised as underweight [<18.5 kg/m^2], normal weight [18.5–< 25.0 kg/m^2], overweight [25.0–< 30.0 kg/m^2], or obese [≥30.0 kg/m^2]).

Statistical analysis

A complete case analysis was conducted on 150,969 participants. Based on their frequency distribution, fruit and vegetable consumption were categorised as quartiles (Q). Descriptive statistics for baseline characteristics were computed for the overall sample and according to fruit and vegetable consumption, both as separate and combined categories. Crude and adjusted hazard ratios (HRs) with 95 % confidence intervals (CIs) were estimated for all categories of fruit and vegetable consumption (combined fruit and vegetables, total fruit, total vegetables, cooked vegetables, raw vegetables) by using Cox proportional hazards models, with the lowest intake category used as a reference category. To test the statistical significance for trends (measured by probability [*P*] for trends) in the associations across increasing quartiles of fruit and vegetable intake, quartiles of intake were replaced with a continuous variable calculated from the respective midpoints of the quartiles in the Cox proportional hazard models. Three models were tested for each exposure variable: Model 1 was an unadjusted model; Model 2 was minimally adjusted for age and sex; Model 3 was adjusted for age, sex, education level, marital status, location of residence, socio-economic status, smoking status, physical activity categories, multi-vitamin use, processed meat consumption, diabetes and body mass index categories. Analyses of vegetable consumption were adjusted for fruit consumption (and vice versa).

As suggested by previous studies, variables including age, sex, education level, smoking and body mass index could potentially moderate the association between fruit and vegetable consumption and all-cause mortality [9, 12]. Furthermore, lifestyle factors, such as fruit and vegetable consumption, may have differential effects on those with different health status. Therefore, in Model 3, we tested for potential effect modification by age group (45–59 years; 60–74 years; ≥75 years), sex, education level, smoking status, body mass index categories, and self-rated health. Any significant ($P < 0.05$) interactions were further explored in stratified analyses. Finally, due to the relatively short follow-up, an additional sensitivity analysis was conducted by repeating the analysis on those with at least two years of follow-up to test for occult disease at baseline. Data were analysed using SAS version 9.3 (SAS Institute Inc.) and the significance level was set at 0.05.

Results

Participant characteristics

Among 150,969 participants followed up for an average of 6.2 (standard deviation [SD]: 1.0) years and a total of 933,538 person-years, 6,038 (4 %) died. Overall, the mean age (SD) of participants at baseline was 60.0 (10.1) years, more than half (55.2 %) of participants were women, more than a quarter (27 %) completed college or university, more than three quarters (77.7 %) were in a married/de facto relationship, and 54.7 % lived in regional/remote areas. The mean intakes (SD) for fruit, vegetables, and both fruit and vegetables, were respectively: 1.9 (1.4), 3.9 (2.6), and 5.8 (3.3) servings/day. More than half (60.5 %) of the sample (48.6 % of men; 70.2 % of women) met the World Health Organization's recommendations of consuming a combination of five serves of fruit and vegetables per day [1]. Baseline characteristics of study participants by categories of fruit and vegetable consumption are presented in Table 1. Compared with participants with lower intakes of fruit and vegetables, those who consumed higher amounts were more likely to be younger, women, in a married/de facto relationship, and living in remote/rural areas. Such participants were also more likely to sleep between 7 to 9 h per day, exercise more than 300 min/week, be non-smokers, non-obese and to perceive themselves in very good or excellent health.

Fruit and vegetable consumption and all-cause mortality

Table 2 shows the HRs for all-cause mortality according to categories of fruit and vegetable intake. The combined consumption of fruit and vegetables was inversely related to all-cause mortality in all models. In the fully adjusted model, this association was substantially attenuated compared with the unadjusted model (Q4 versus Q1; HR: 0.76; 95 % CI: 0.71, 0.81; *P* for trend < 0.0001) but remained significant (Q4 versus Q1; HR: 0.90; 95 % CI: 0.84, 0.97; *P* for trend = 0.002). The highest risk reduction was observed with the highest consumption quartile (Q4: 7 serves or more of fruit and vegetables/day).

Table 1 Baseline characteristics of 150,969 participants from the 45 and Up Study by frequency of fruit and vegetable intakes[a]

		Quartiles of fruit intake[b]				Quartiles of vegetable intake[b]				Quartiles of combined fruit and vegetable intake[b]			
Variable	Overall	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of subjects	150,969	12,960	50,766	50,111	37,132	54,562	24,460	40,979	30,968	37,467	43,004	34,779	35,719
Mean servings per day (SD)		0.001 (0.02)	1.01 (0.05)	2.00 (0.00)	3.73 (1.46)	1.65 (0.57)	2.99 (0.08)	4.39 (0.49)	7.83 (2.61)	2.44 (0.80)	4.49 (0.50)	6.44 (0.50)	10.27 (3.12)
Age group (%)													
45 to 59 years	56.5	64.5	58.3	55.6	52.4	59.1	59.4	55.2	51.3	59.9	59.4	55.2	50.7
60 to 74 years	33.5	28.5	32.0	34.3	36.3	30.7	31.1	35.2	38.0	30.1	31.2	35.1	38.2
≥75 years	10.0	7.1	9.7	10.1	11.3	10.3	9.4	9.6	10.7	10.0	9.4	9.7	11.1
Women (%)	55.2	41.2	48.0	61.4	61.6	40.5	55.3	65.7	67.1	36.6	54.1	64.8	66.7
College or higher education (%)	27.0	18.0	26.0	28.5	29.5	26.1	31.9	29.0	22.1	24.1	29.8	29.1	24.7
Married/de facto (%)	77.7	73.0	78.8	78.6	76.8	74.7	78.6	80.3	78.9	74.3	78.4	79.9	78.4
Location of residence													
Major city (%)	45.3	42.2	44.5	45.5	47.0	47.9	47.6	44.3	40.1	46.9	46.9	44.9	41.9
Rural/remote (%)	54.7	57.8	55.5	54.5	53.0	52.1	52.4	55.7	59.9	53.1	53.1	55.1	58.1
Socio-economic status (SEIFA-IRSD) (%)													
Quintile 1 (most disadvantaged)	19.1	22.6	20.0	18.1	17.9	19.1	17.5	18.3	21.3	20.0	18.2	18.1	20.2
Quintile 2	19.1	20.7	19.0	19.1	18.8	18.8	18.4	19.1	20.2	19.0	18.7	18.9	19.8
Quintile 3	21.0	21.4	21.1	21.0	20.5	20.6	20.1	21.1	22.2	20.9	20.2	21.2	21.7
Quintile 4	20.1	19.4	19.6	20.5	20.6	20.0	20.6	20.6	19.3	19.8	20.4	20.5	19.7
Quintile 5 (least disadvantaged)	20.7	15.9	20.2	21.4	22.2	21.4	23.4	21.0	17.0	20.3	22.5	21.3	18.6
Current smoking (%)	7.5	21.2	9.2	5.0	3.8	9.9	6.6	5.8	6.2	12.7	7.0	5.3	4.9
Hours of sleep (%)													
<7 h/day	15.1	19.8	15.2	13.9	15.0	16.9	13.9	13.5	15.0	17.3	14.7	13.6	14.7
7–9 h/day	67.6	60.7	66.9	69.5	68.6	66.3	69.1	68.8	67.3	65.0	68.7	68.9	68.0
≥9 h/day	17.3	19.6	17.8	16.7	16.4	16.7	17.0	17.7	17.7	17.7	16.6	17.5	17.3
Physical activity category (%)													
10–149 min/week	19.1	29.0	21.9	16.9	14.8	22.9	18.5	16.7	16.1	25.7	19.0	16.0	15.2
150–299 min/week	16.1	17.2	17.2	15.9	14.3	17.0	17.2	15.8	13.8	17.5	17.0	15.8	13.7
≥300 min/week	64.8	53.8	61.0	67.2	70.8	60.0	64.4	67.5	70.1	56.7	64.0	68.1	71.1
Multivitamin use (%)	3.2	2.9	3.3	3.2	3.1	3.3	3.1	2.9	3.1	3.3	3.2	2.9	3.1
Self-rated health (%)													
Excellent	18.3	12.4	15.7	19.2	22.8	15.7	18.7	20.0	20.4	13.8	18.1	20.0	21.7

Table 1 Baseline characteristics of 150,969 participants from the 45 and Up Study by frequency of fruit and vegetable intakes[a] *(Continued)*

Very good	40.6	33.2	40.0	42.2	41.7	38.4	40.8	42.3	42.0	36.8	41.1	42.6	42.0
Good	31.4	37.0	33.7	30.2	27.7	34.0	31.4	29.5	29.1	35.9	31.6	29.3	28.3
Fair	8.5	14.7	9.3	7.4	6.9	10.4	8.1	7.2	7.6	11.7	8.2	7.3	7.0
Poor	1.2	2.7	1.3	0.9	0.9	1.5	1.0	0.9	1.0	1.8	1.1	0.8	0.9
BMI category (%)													
Underweight and normal weight (≤18.5 to <25.0 kg/m^2)	39.0	34.9	37.7	39.1	42.1	37.3	41.1	40.3	38.7	36.5	39.3	40.3	40.0
Overweight (25.0 to <30.0 kg/m^2)	39.4	39.3	40.5	39.2	38.0	41.5	38.8	37.9	37.9	41.6	39.8	38.0	37.8
Obese (≥30.0 kg/m^2)	21.6	25.8	21.8	21.7	19.9	21.2	20.1	21.8	23.4	21.8	21.0	21.7	22.2
Physician diagnosed diabetes (%)	7.0	5.9	6.4	7.4	7.6	6.9	6.3	6.9	7.7	6.5	6.7	7.0	7.7

Abbreviations: *BMI* body mass index, *min* minutes, *IRSD* Index of Relative Socio-economic Disadvantage, *Q* quartile of intake, *SD* standard deviation, *SEIFA* Socio-Economic Indexes For Areas

[a]Data are presented as means (SD) or percentages (%)

[b]The quartiles of intake for fruit and vegetables (servings/day) were as follows: Fruit: Q1: <1.0; Q2: 1.0 to <2.0; Q3: 2.0 to <2.3; Q4: ≥2.3. Vegetables: Q1: ≤2.0; Q2: 2.0 to ≤3.0; Q3: 3.0 to ≤5.0, Q4: >5.0. Fruit and vegetables combined: Q1: <4.0; Q2: 4 to ≤5.0; Q3: >5.0 to ≤7.0; Q4: >7.0

Table 2 Hazard ratios and 95 % confidence intervals of all-cause mortality by quartiles of intake for fruit and vegetables ($n = 150,969$)

	Quartiles[a]								
	Q1		Q2		Q3		Q4		P for trend
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	
Fruit and vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.80	0.75,0.85	0.70	0.65,0.75	0.76	0.71,0.81	<0.0001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.89	0.83,0.95	0.79	0.73,0.85	0.77	0.72,0.83	<0.0001
Model 3[c] (adjusted)	1.0	Reference	0.99	0.93,1.06	0.92	0.86,0.99	0.90	0.84,0.97	0.002
Fruit intake[a]									
Model 1 (crude)	1.0	Reference	0.91	0.83,1.00	0.78	0.72,0.86	0.78	0.71,0.85	<0.001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.75	0.69,0.83	0.66	0.60,0.72	0.62	0.56,0.68	<0.001
Model 3[c] (adjusted)	1.0	Reference	0.91	0.83,0.99	0.86	0.78,0.94	0.84	0.76,0.93	0.001
Vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.78	0.72,0.84	0.71	0.66,0.75	0.79	0.74,0.85	<0.0001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.87	0.81,0.94	0.81	0.76,0.87	0.82	0.77,0.88	<0.0001
Model 3[c] (adjusted)	1.0	Reference	0.95	0.88,1.02	0.92	0.86,0.99	0.93	0.87,1.00	0.017
Cooked vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.74	0.68,0.80	0.87	0.81,0.94	0.88	0.81,0.95	0.004
Model 2[b] (age, sex adjusted)	1.0	Reference	0.86	0.80,0.93	0.89	0.83,0.97	0.80	0.74,0.86	<0.0001
Model 3[c] (adjusted)	1.0	Reference	0.92	0.85,1.00	0.98	0.90,1.06	0.87	0.80,0.95	0.003
Raw vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.62	0.57,0.66	0.56	0.50,0.61	0.65	0.59,0.72	<0.0001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.76	0.70,0.82	0.76	0.69,0.84	0.77	0.70,0.85	0.0005
Model 3 (adjusted)	1.0	Reference	0.87	0.81,0.94	0.92	0.84,1.02	0.94	0.85,1.04	0.793

Abbreviations: *CI* confidence interval, *HR* hazard ratio, *Q* quartile

[a]The quartiles of intake for fruit and vegetables (servings/day) were as follows: Fruit and vegetables combined: Q1: <4.0; Q2: 4 to ≤ 5.0; Q3: 5.0 to ≤7.0; Q4: >7.0. Fruit: Q1: <1.0; Q2: 1.0 to <2.0; Q3: 2.0 to <2.3; Q4: ≥2.3. Vegetables: Q1: ≤2.0; Q2: 2.0 to ≤3.0; Q3: 3.0 to ≤5.0, Q4: >5.0. Cooked vegetables: Q1: ≤1.0; Q2: 1.0 to ≤2.0; Q3: 2.0 to ≤3.0, Q4: >3.0. Raw vegetables: Q1: <1.0; Q2: 1.0 to <1.3; Q3: 1.3 to ≤ 2.0; Q4: >2.0

[b]Model 2 was adjusted for age (continuous) and sex

[c]Model 3 was adjusted for age (categorical), sex, education level, marital status, location of residence, socio-economic status, smoking status, physical activity categories, multi-vitamin use, processed meat consumption, diabetes and body mass index categories. Any significant ($P < 0.05$) interactions (shown in Table 3) with age group, sex, education level, body mass index categories and smoking status, were included in this model. The model for fruit was adjusted for vegetable intake and vice versa

Similarly, when fruit consumption was considered separately, there was an inverse association with all-cause mortality in all models. Participants in the top quartile had a significantly lower risk of all-cause mortality than those in the bottom quartile (fully adjusted model: HR: 0.84; 95 % CI: 0.76, 0.93; P for trend ≤ 0.001). Consumption of total vegetables, as well as separate consumption of cooked and raw vegetables, was associated with a lower risk of all-cause mortality in the unadjusted and minimally adjusted models (all P for trend < 0.05). In the fully adjusted models, these associations were markedly attenuated compared with the unadjusted models, but remained statistically significant for total vegetables and cooked vegetables only (P for trend < 0.05). The association with raw vegetable consumption showed estimates (and CIs) that were consistent with those for cooked vegetables but these findings were not significant. The sensitivity analyses conducted on participants with at least two years of follow-up showed similar results that were slightly attenuated (Appendix: Table 4).

Effect modification

Significant ($P < 0.05$) effect modifiers of the association between fruit and vegetable intake and risk of all-cause mortality included sex and age group (Table 3). Consumption of fruit and vegetables combined, and separate consumption of vegetables, were inversely related with all-cause mortality in women but not in men. Consumption of fruit was associated with lower HRs in individuals aged between 60 to 74 years compared to other age groups.

Discussion

To our knowledge, this is the first prospective cohort study in Australia and one of the largest worldwide to explore the relationship between fruit and vegetable consumption and all-cause mortality. Consumption of fruit and vegetables combined was inversely related to all-cause mortality in this large cohort of middle-aged and older Australian adults. After adjustment for age and

Table 3 Hazard ratios and 95 % confidence intervals of all-cause mortality by quartiles of intake for fruit and vegetables by effect modifiers

Effect value for significant interactions	Quartiles[a]								P for interaction
	Q1		Q2		Q3		Q4		
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	
Fruit and vegetable intake[a]									
Male	1.0	Reference	1.03	(0.95,1.12)	0.97	(0.88,1.06)	1.01	(0.92,1.11)	0.002
Female	1.0	Reference	0.89	(0.79,0.99)	0.80	(0.71,0.91)	0.76	(0.67,0.85)	
Fruit intake[a]									
45 to 59 years	1.0	Reference	0.83	(0.68,1.01)	0.88	(0.72,1.08)	0.86	(0.69,1.07)	0.045
60 to 74 years	1.0	Reference	0.84	(0.73,0.98)	0.80	(0.68,0.93)	0.82	(0.69,0.96)	
≥75 years	1.0	Reference	1.13	(0.98,1.30)	1.05	(0.91,1.21)	0.98	(0.84,1.13)	
Vegetable intake[a]									
Male	1.0	Reference	0.94	(0.86,1.04)	0.94	(0.86,1.03)	1.04	(0.94,1.14)	0.012
Female	1.0	Reference	0.94	(0.77,1.14)	0.84	(0.76,0.93)	0.82	(0.73,0.92)	

Abbreviations: *CI* confidence interval, *HR* hazard ratio, *Q* quartile

[a]The quartiles of intake for fruit and vegetables (servings/day) were as follows: Fruit and vegetables combined: Q1: <4.0; Q2: 4 to ≤ 5.0; Q3: 5.0 to ≤7.0; Q4: >7.0. Fruit: Q1: <1.0; Q2: 1.0 to <2.0; Q3: 2.0 to <2.3; Q4: ≥2.3. Vegetables: Q1: ≤2.0; Q2: 2.0 to ≤3.0; Q3: 3.0 to ≤5.0, Q4: >5.0

sex, this association was attenuated by approximately 6 %. Following adjustment for socio-economic, lifestyle and health-related factors, the association was attenuated further by approximately 12 % but remained statistically significant. Individual consumption of fruit or vegetables was associated with reduced mortality from all-causes in all models. Vegetables consumed cooked or raw, were also associated with a lower risk of all-cause mortality in unadjusted and minimally adjusted models. However, after adjustment for all other covariates, cooked vegetables remained significantly related to a lower risk of all-cause mortality. While the association of raw vegetables with all-cause mortality was similar to that of cooked vegetables, it did not remain statistically significant. Sex and age group were significant effect modifiers of the relationship between fruit and vegetable consumption and all-cause mortality.

Findings from the present study are in line with those from previous prospective cohort studies which have mostly found a significant inverse relationship between fruit and vegetable intake (considered separately or combined) and all-cause mortality [9, 18–20]. A recent meta-analysis of prospective cohort studies showed that pooled hazard ratios of all-cause mortality were 0.95 (95 % confidence interval: 0.92, 0.98; $P = 0.001$) for an increment of one serving a day of fruit and vegetables, 0.94 (95 % CI: 0.90, 0.98; $P = 0.002$) for fruit, and 0.95 (95 % CI: 0.92, 0.99; $P = 0.006$) for vegetables [8]. In our study, the protective effect of consuming both fruit and vegetables was slightly smaller. Differences in findings could be due to a number of factors that vary between studies including measures of fruit and vegetable consumption, covariate adjustment, follow-up time and cohort characteristics. Previous studies generally had longer follow-up periods and more detailed dietary measures [8]. However, in their meta-analysis, Wang et al. found that study location, sex, sample size, study quality and duration of follow-up had little impact on the association between fruit and vegetable intake and all-cause mortality [8].

The meta-analysis by Wang and colleagues also showed a dose–response relationship up to a threshold of five servings/day for fruit and vegetables combined, two servings/day for fruit, and three servings/day for vegetables [8]. There was no further reduction in mortality risk beyond these thresholds. In the present study, protective effects on mortality risk were observed starting with the second quartile of consumption (4 to ≤5 servings/day of fruit and vegetables, 1 to <2 servings/day of fruit and 2 to ≤3 servings/day of vegetables). However, with the exception of vegetable consumption which appeared to reach a threshold at 3 to ≤5 servings/day beyond which there was no further risk reduction, findings from the present study differed from those of the meta-analysis. For the consumption of fruit and vegetables combined and that of fruit only, the point estimates decreased with increasing serves, with the highest risk reductions achieved with 7 serves/day or more of fruit and vegetables, and 2.3 serves/day or more of fruit. These findings are in agreement with a recent study conducted in the United Kingdom which found a strong inverse association between combined fruit and vegetable consumption and all-cause mortality in 65,226 participants aged 35 years and over, with highest benefits seen with 7 serves/day or more of fruit and vegetables, 3 to <4 serves/day of fruit and 3 serves/day or more of vegetables [19]. It seems that current Australian recommendations to consume two serves of fruit (150 g each) and five serves of vegetables (75 g each) per day are appropriate [21]. However, more

efforts at promoting fruit and vegetable consumption are needed as approximately only 6–8 % of the NSW population aged 45 years and over currently meet Australian recommendations for fruit and vegetable intake [22].

To date, several observational studies have investigated the differential effects of consuming cooked versus raw vegetables on all-cause mortality. Cooking can alter the physical structure and properties of bio-active compounds (such as phytochemicals, vitamins, minerals and fibre) contained in vegetables, and thereby change their physiologic effect, in a potentially beneficial or less desirable way for health [13]. For example, the bioavailability of compounds that may act as antioxidants can either be enhanced (e.g. certain carotenoids such as carotenes in carrots and lycopene in tomatoes) or decreased (e.g. vitamin C) by heat treatment. Although results are still preliminary, several observational studies found that raw vegetable consumption was more protective against mortality than cooked vegetable consumption [9, 13]. The results of this study show similar relationships of cooked and raw vegetables to mortality. It should be noted that power was limited for raw vegetable consumption in the current study, which made it difficult to detect significant differences between quartiles. Further studies examining the effects of raw versus cooked vegetables on mortality risk are needed to explore these preliminary findings.

While there were some significant effect modifiers of the association between fruit and vegetable consumption and all-cause mortality identified in the current study, these findings should be interpreted with caution. Consumption of fruit and vegetables combined, as well as separate consumption of vegetables only, were inversely related with risk of all-cause mortality in women but not in men. To date, sex differences in these associations have not been clearly established. The meta-analysis by Wang et al. as well as several previous studies did not observe significant sex differences [8, 12, 18, 23, 24]. However, in the large European Prospective Investigation into Cancer and Nutrition cohort study, while there were no significant sex differences for the consumption of fruit and vegetables combined or the individual consumption of vegetables, the individual consumption of fruit was inversely associated with risk of all-cause mortality in women but not in men [9]. As suggested by the authors of that study, possible explanations for the discrepancy in findings include residual confounding, a finding due to chance, or a true biological difference, although a mechanism for such a difference is not apparent. Women may also report their intake of fruit and vegetables more accurately than men. In the few studies that stratified analyses by age, there was no significant effect modification by age [12, 25]. Clearly, further evidence is needed to support findings about potential effect modifiers and the underlying mechanisms remain to be elucidated.

Strengths and limitations

The main strengths of this study include a large population-based sample, high quality record linkage and the inclusion of multiple socio-demographic, health-related and dietary covariates. The processing of vegetables (i.e., whether vegetables were cooked or raw) was also considered. The prospective nature of the study helped minimise recall bias.

This study had several limitations including the relatively short follow-up time which may have been insufficient to observe long-term effects of fruit and vegetable intake. Although the short dietary questions used in this study are appropriate for large-scale studies, it is possible that the self-reported consumption may not accurately capture true consumption. Most previous studies have used more detailed dietary methods such as food frequency questionnaires and food records, although these are also prone to measurement error [8]. One major limitation of our brief questionnaire in comparison with more detailed questionnaires such as food frequency questionnaires, is that we did not measure the specific fruits and vegetables consumed. Examining the roles of different types of fruit and vegetables could be important as some kinds of fruit and vegetables could be more beneficial than others. In addition, the dietary questions were asked only at baseline and may not reflect the long-term habitual patterns of dietary behaviour. As this is an observational study, residual confounding could also be of concern. We tried to minimise this by adjusting for multiple covariates and by repeating the analyses among those with at least two years of follow-up data. Due to the limited number of dietary questions in the 45 and Up Study questionnaire, we could not assess other food items beyond processed meat as potential confounders. Future studies could consider including more detailed dietary measures differentiating between subgroups of vegetables, whether vegetables are consumed raw or cooked, cooking method, and collecting repeated dietary measures over time to establish long-term patterns of fruit and vegetable consumption.

Conclusions

In this large cohort of middle-aged and older Australian adults, consumption of fruit and vegetables was inversely associated with all-cause mortality during 6.2 years of follow-up. Findings from this study support recommendations to consume a high amount of fruit and vegetable consumption. The association of raw versus cooked vegetables in relation to mortality requires further investigation.

Appendix

Table 4 Hazard ratios and 95 % confidence intervals of all-cause mortality by quartiles of intake for fruit and vegetables for sensitivity analyses conducted on 149,787 participants with at least two years of follow-up

	Quartiles[a]								
	Q1		Q2		Q3		Q4		P for trend
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	
Fruit and vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.81	0.76, 0.88	0.74	0.68, 0.80	0.80	0.74, 0.86	<0.0001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.90	0.84, 0.97	0.83	0.76, 0.90	0.80	0.74, 0.87	<0.0001
Model 3[c] (adjusted)	1.0	Reference	1.00	0.93, 1.08	0.96	0.88, 1.04	0.93	0.86, 0.93	0.07
Fruit intake[a]									
Model 1 (crude)	1.0	Reference	0.90	0.81, 0.99	0.79	0.71, 0.87	0.79	0.71, 0.88	<0.001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.74	0.67, 0.82	0.66	0.59, 0.73	0.62	0.56, 0.69	<0.001
Model 3[c] (adjusted)	1.0	Reference	0.88	0.80, 0.98	0.84	0.76, 0.94	0.83	0.74, 0.93	0.003
Vegetable intake[a]									
Model 1 (crude)	1.0	Reference	0.82	0.75, 0.89	0.73	0.68, 0.79	0.84	0.78, 0.91	<0.0001
Model 2[b] (age, sex adjusted)	1.0	Reference	0.91	0.83, 0.99	0.84	0.78, 0.90	0.87	0.80, 0.94	<0.0001
Model 3[c] (adjusted)	1.0	Reference	0.98	0.90, 1.07	0.94	0.87, 1.02	0.98	0.90, 1.06	0.309

Abbreviations: *CI* confidence interval, *HR* hazard ratio, *Q* quartile

[a]The quartiles of intake for fruit and vegetables (servings/day) were as follows: Fruit and vegetables combined: Q1: <4.0; Q2: 4 to ≤ 5.0; Q3: 5.0 to ≤7.0; Q4: >7.0. Fruit: Q1: <1.0; Q2: 1.0 to <2.0; Q3: 2.0 to <2.3; Q4: ≥2.3. Vegetables: Q1: ≤2.0; Q2: 2.0 to ≤3.0; Q3: 3.0 to ≤5.0, Q4: >5.0

[b]Model 2 was adjusted for age (continuous) and sex

[c]Model 3 was adjusted for age (categorical), sex, education level, marital status, location of residence, socio-economic status, smoking status, physical activity categories, multi-vitamin use, processed meat consumption, diabetes and body mass index categories. The model for fruit was adjusted for vegetable intake and vice versa

Abbreviations

CI: confidence interval; HR: hazard ratio; NSW: State of New South Wales; P: probability; Q: quartile; SD: standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BN, AB, JG and DD participated in the design of the study. JG carried out the statistical analyses. BN, AB and DD helped draft the manuscript. All authors helped with the interpretation of the data and revised the manuscript critically for important intellectual content. All authors read and approved the manuscript.

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3.5 CONCLUDING SUMMARY FOR THIS CHAPTER AND KNOWLEDGE GAINED FROM THIS STUDY

To our knowledge, this was the first prospective cohort study to examine the association between fruit and vegetable consumption, including raw and cooked vegetable consumption, and all-cause mortality in Australia. There was an inverse association between fruit and vegetable consumption, considered separate or combined, and all-cause mortality among middle-aged and older Australians. Findings were in support of Australian dietary guidelines as reductions in mortality were seen up to seven servings of fruit and vegetables per day. Vegetables consumed raw or cooked were associated with a lower risk of mortality; however, the association with raw vegetables was not significant after adjustment for socio-economic, lifestyle and health-related factors. Fruit and vegetable consumption was found to be protective in women but not in men. Additional research is needed to confirm observed differences between men and women, and to explore whether raw versus cooked vegetable consumption have differential effects on health and mortality. Given the limited nature of the dietary questions used in this study, future studies could benefit from more detailed dietary methods such as food frequency questionnaires.

3.6 REFERENCES

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CHAPTER FOUR:

Incident type 2 diabetes in a large Australian cohort study: Does physical activity or sitting time alter the risk associated with body mass index?

4.1 PREFACE TO THE CHAPTER

This chapter presents findings from a peer-reviewed paper that examined the separate and combined effects of overweight/obesity, physical activity and sitting time on incident type 2 diabetes in the 45 and Up Study cohort. A gender-specific analysis was also conducted as an extension to this paper and findings from this analysis are presented in **Appendix 1**. This chapter, consisting of the published paper, addresses specific aims #2 and #5 of this thesis as described in Chapter 1. Dissemination of this research and author contributions for this paper are described below.

4.2 RESEARCH DISSEMINATION

The research presented in this chapter has been disseminated as follows:

Published peer-reviewed paper

Nguyen B, Bauman A, Ding D. Incident type 2 diabetes in a large Australian cohort study: Does physical activity or sitting time alter the risk associated with body mass index? *Journal of Physical Activity and Health* 2017; 14(1): 13-19. Available from: http://doi.org/10.1123/jpah.2016-0184

Impact factor: 1.723

Citations (based on Google Scholar): 5

Conference presentations

Nguyen B, Bauman A, Ding D. Incident type 2 diabetes in a large Australian cohort study: Does physical activity or sitting time alter the risk associated with body mass index? *6th*

International Society for Physical Activity and Health (ISPAH) International Congress on Physical Activity and Public Health, Bangkok, Thailand, 2016. [Oral presentation]

Nguyen B, Bauman A, Ding D. Incident type 2 diabetes in a large Australian cohort study: Does physical activity or sitting time alter the risk associated with body mass index? *Sax Institute 45 and Up Study Collaborators' Annual Meeting,* Sydney, Australia, 2016. [Oral presentation] – **Selected for 45 and Up Study media press release and media launch event resulting in television (SBS and Channel 9 news), multiple radio and newspaper interviews.**

Informing policies/guidelines

Findings from this paper were included in the latest (2018) American Physical Activity Guidelines Advisory Committee Scientific report.[1]

4.3 AUTHOR ATTRIBUTION STATEMENT

I, Binh Nguyen, was responsible for designing the study, analysing and interpreting data, writing drafts of the manuscript, submitting the manuscript, responding to reviewers' comments, and coordinating submission and publication of the manuscript.

My co-authors, A. Bauman and D. Ding, helped to design the study, draft the manuscript, interpret data, and revise the manuscript critically for important intellectual content.

All authors have read and approved the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.

Signature:

Dr. Ding (Melody) Ding

4.4 PAPER IN PUBLISHED FORMAT

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Human Kinetics
ORIGINAL RESEARCH

Incident Type 2 Diabetes in a Large Australian Cohort Study: Does Physical Activity or Sitting Time Alter the Risk Associated With Body Mass Index?

Binh Nguyen, Adrian Bauman, Ding Ding

Purpose: To examine the combined effects of body mass index (BMI), physical activity (PA) and sitting on incident type 2 diabetes mellitus (T2DM) among Australian adults. **Methods:** A sample of 29,572 adults aged ≥45 years from New South Wales, Australia, completed baseline (2006–2008) and follow-up (2010) questionnaires. Incident T2DM was defined as self-reported, physician-diagnosed diabetes at follow-up. BMI was categorized as normal/overweight/obese. PA was tertiled into low/medium/high. Sitting was dichotomized as higher/lower sitting (≥ 8 hours/day or < 8 hours/day). Odds ratios (OR) were estimated for developing T2DM using logistics regression for individual and combined risk factors, and data stratified by BMI categories. **Results:** During a mean 2.7 (SD: 0.9) years of follow-up, 611 (2.1%) participants developed T2DM. In fully adjusted models, BMI was the only independent risk factor for incident T2DM. In stratified analyses, the association between BMI and T2DM did not differ significantly across sitting or PA categories. Overweight/obese individuals with high PA and lower sitting had higher odds of incident T2DM than normal counterparts with low PA and higher sitting. **Conclusions:** High PA/low sitting did not attenuate the risk of T2DM associated with overweight/obesity. Maintaining a healthy weight, by adopting healthy lifestyle behaviors, is critical for T2DM prevention.

Keywords: diabetes mellitus, sedentary behavior, obesity

Type 2 diabetes mellitus (T2DM) has become a public health burden worldwide, with 1 in 10 adults estimated to have diabetes by 2040.[1] The epidemic rise in T2DM is closely linked to lifestyle changes and the rapid increase in overweight and obesity.[2] Lifestyle modification could lead to considerable risk reduction and is a high priority for T2DM prevention.[2] Yet, the relative importance and combined influence of lifestyle risk factors for developing T2DM need further research, as the current evidence is based on relatively few studies.

Obesity and physical inactivity are established independent risk factors of T2DM, with growing evidence from prospective studies suggesting that obesity may be more important than physical inactivity for T2DM prevention.[3–5] A recent meta-analysis has shown that a high body mass index (BMI), even with high physical activity (PA), was a greater risk factor for incident T2DM than a normal BMI with low PA.[3] These findings were based on 6 prospective studies that mostly included middle-aged and older adults.

Other lifestyle risk factors could play a role in the development of T2DM. Findings from recent systematic reviews and meta-analyses, derived mainly from prospective studies, have shown that sedentary behavior may be associated with an increased risk of T2DM among adults of various ages.[6–9] However, these findings were based on a limited number of studies, most of which used television viewing instead of total sitting time, and some did not adjust for PA. Further, it is unclear whether the association between sitting and T2DM is independent of BMI.[7,10,11] Overall, the joint effects of levels of BMI, PA and sitting time on incident T2DM have seldom been studied.[10] Examining to what extent PA and sitting time may offset health risks associated with overweight/obesity can help prioritize public health strategies for T2DM prevention.

With an aging population and a higher life expectancy, older people are representing a larger proportion of the world's population, and together with an increasing burden of chronic diseases, could pose a global public health challenge.[12] Chronic disease prevention efforts are vital as population aging is strongly linked with the global epidemic of chronic diseases. Hence, understanding how lifestyle risk factors interact with each other in the context of T2DM prevention is primordial among middle-aged and older adults. The aims of this paper are to examine the combined effects of a) BMI and PA level; b) BMI, PA level, and sitting time on the incidence of T2DM in a large cohort of middle-aged and older Australian adults. Based on existing evidence, we hypothesized that PA would attenuate the BMI-associated risk of developing T2DM while the effects of sitting time remained to be explored.

Methods

Study Population

The baseline data were from the Sax Institute's 45 and Up Study, a large-scale (n = 267,153) population-based study of men and women aged 45 years and over, randomly sampled from New South Wales (NSW), Australia. This study has been described in detail elsewhere.[13] Eligible participants completed a mailed baseline questionnaire (2006–2008). In 2010, follow-up questionnaires (Social, Economic, and Environmental Factor [SEEF] Study) were

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mailed to the first 100,000 participants of the 45 and Up Study, with 60,404 respondents. Participants reporting any of the following at baseline were excluded: diabetes and/or taking diabetes medications (n = 4899), physician-diagnosed cancer (other than nonmelanoma skin cancer; n = 8429) or cardiovascular disease (n = 8790), severe physical functional limitations[14] (n = 5002). Participants that were underweight at baseline (BMI < 18.5 kg/m^2; n = 702), those that specified having "type 1 diabetes" at follow-up (n = 12) and those with missing data for any of the independent variables (n = 2747 for BMI, n = 820 for PA, n = 2037 for sitting time) were also excluded. The final analytic sample included 29,572 participants (13,416 men, 16,156 women). The 45 and Up Study was granted ethical approval by the University of NSW Human Research Ethics Committee [HREC] (reference HREC 05035/ HREC 10186) and the SEEF study by the University of Sydney HREC (reference 10-2009/12187).

Measurements

Outcome. Questionnaires are available at http://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/. Incidence of T2DM, based on self-reported data, was defined as not having physician-diagnosed diabetes nor taking diabetes medications at baseline and reporting a diagnosis of diabetes at follow-up. Self-reported diagnosis of diabetes in the 45 and Up Study has been validated previously, with high sensitivity and specificity compared with linked administrative data.[15]

Independent Variables. BMI was derived from self-reported height and weight, which has been previously validated in this cohort,[16] and was categorized as: normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30.0 kg/m^2). PA, measured using validated questions from the Active Australia Survey, was calculated as the sum of time spent on walking, moderate-intensity and vigorous-intensity (weighted by 2) PA in the past week.[17] PA was categorized into tertiles: low (0 to <300 minutes [min]/week), medium (300 to <660 min/week) and high (≥660 min/week). Using quantiles ensures that the range in exposure is captured evenly across distribution categories, which facilitates comparison between different levels of PA among the study cohort, and has been previously used in other large known cohort studies.[18,19] It has been used in several other large renowned cohort studies Average daily sitting time was dichotomized as ≥8 hours/day (higher sitting) and <8 hours/day (lower sitting) based on previous analysis.[20]

Covariates. Covariates included baseline sex, age (45–54, 55–64, 65–74, ≥75 years), country of birth (Australia/New Zealand, Europe, Middle East, Asia, North America, other), education (≤10 years of schooling, high school/trade apprenticeship/certificate/diploma, university degree/ higher), a family history of T2DM (yes/no) and follow-up time.[21]

Statistical Analysis

First, we examined the association between 3 independent variables and T2DM individually in unadjusted models and models adjusted for covariates and lifestyle risk factors. Then, to examine whether PA/sitting was associated with T2DM regardless of weight status, we reanalyzed data stratified by BMI categories. Normal weight and lower sitting were respectively selected as reference categories for BMI and sitting time as they were hypothesized to be the lowest-risk categories. Although we expected that the highest level of PA would provide greater health benefits than other PA levels, the lowest level of PA was selected as the reference category to enable comparison between the lowest (<300 min/week) and medium levels of PA (300 to <660 min/week). We tested effect modification by PA and sitting by fitting interaction terms. Finally, to compare across all combinations of BMI, PA, and sitting, we divided participants into 9 mutually exclusive categories based on BMI and PA levels and 18 categories based on BMI, PA and sitting levels. The category with the hypothesized healthiest combination of lifestyle risk factors (ie, normal weight-high PA-[low sitting]) was chosen as the reference category. To increase statistical power, missing data for any covariate (n = 275 for country of birth, n = 434 for education, n = 1 for family history of T2DM) were analyzed using a missing indicator approach. Logistic regression analysis was conducted using SPSS version 22 (IBM Corp., Armonk, NY), and a significance level of 0.05.

Results

Of 29,572 participants without diabetes at baseline, 611 (2.1%) reported T2DM at follow-up (mean [standard deviation, SD]: 2.7 [0.9] years). Overall, the mean (SD) age of participants was 58.9 (9.2) years, more than half (54.6%) were women, and nearly a third (31.6%) had a university degree/higher (Table 1). The majority were normal weight (42.1%) or overweight (41.0%), physically active (mean [SD]: 576 [478] min/week) and sat < 8 hours/day (84.6%).

Table 2 shows the unadjusted and adjusted odds ratios (OR) for incident T2DM by levels of individual risk factors. Compared with normal weight subjects, being overweight/obese was significantly associated with higher odds of developing T2DM in unadjusted and adjusted models. Compared with the low PA tertile, the odds of incident T2DM were significantly lower in higher PA tertiles in the unadjusted model only. The OR were not significantly different between higher and lower sitting time in both models.

In stratified analyses, OR were not different between BMI categories for different levels of PA and sitting (Table 3). Overall, there were no significant interactions between BMI categories and PA / sitting.

When comparing across all combinations of PA, sitting, and BMI levels, normal-weight participants who had low levels of PA (and higher sitting) had lower risk of T2DM than overweight or obese participants with high PA (and lower sitting; Table 4), further suggesting that overweight/obesity is a more important risk factor of T2DM, and that its effect on T2DM could not be offset by high PA or a combination of high PA and lower sitting.

Discussion

To our knowledge, this study is among the first to investigate whether the BMI-associated risk of developing T2DM is offset by PA and sitting. In this large cohort of middle-aged and older Australians, overweight/obesity was a more important risk factor for developing T2DM compared with PA and sitting. Overweight and obese participants had respectively 2 and 5 times the odds of developing T2DM compared with normal weight counterparts, even after adjustment for PA and sitting time. The risk of developing T2DM associated with high BMI was neither attenuated by PA nor sitting time.

Although there is increasing evidence that individuals with a high BMI and good level of aerobic fitness have lower risks of all-

Table 1 Baseline Characteristics by Diabetes Status at Follow-up (n = 29,572; 2006–2010)[a]

Variable	All	Diabetes status[b]	
		No diabetes	Diabetes
Number of subjects	29,572	28,961	611
Mean (SD) follow-up time (years)	2.7 (0.9)	2.7 (0.9)	2.9 (1.0)
Women (%)	54.6	54.8	45.2
Mean (SD) age (years)	58.9 (9.2)	58.9 (9.2)	61.1 (9.5)
Age group (%)			
45 to 54 years	40.2	40.4	30.6
55 to 64 years	35.2	35.2	35.0
65 to 74 years	17.9	17.8	26.0
≥75 years	6.7	6.7	8.3
Country of birth (%)			
Australia/New Zealand	79.3	79.3	77.3
Europe	14.9	14.9	15.1
Middle East	0.6	0.6	1.2
Asia	2.6	2.6	3.9
North America	0.9	0.9	0.5
Other	1.7	1.7	2.0
Highest education (%)			
University and higher	31.6	25.0	23.0
High school/TAFE/diploma	43.2	43.2	45.1
≤10 years	25.1	31.8	31.9
Mean (SD) BMI (kg/m^2)	26.3 (4.3)	26.3 (4.2)	29.2 (5.0)
BMI category (%)			
Normal weight (18.5 to <25 kg/m^2)	42.1	42.6	19.5
Overweight (25 to <30 kg/m^2)	41.0	41.0	41.2
Obese (≥30 kg/m^2)	16.9	16.4	39.3
Mean (SD) physical activity time (min/week)[c]	575.7 (478.3)	577.1 (478.9)	511.3 (445.0)
Physical activity tertile (%)			
Low (0 to <300 min/week)	32.2	32.1	38.0
Medium (300 to <660 min/week)	32.8	32.9	31.4
High (≥660 min/week)	34.9	35.0	30.6
Mean (SD) sitting time (hours/day)	5.6 (3.1)	5.6 (3.1)	5.6 (3.0)
Sitting time category (%)			
Lower sitting (<8 hours/day)	84.6	84.6	85.9
Higher sitting (≥8 hours/day)	15.4	15.4	14.1
Mean (SD) MOS-PF score (out of 100)[d]	92.9 (9.4)	92.9 (9.3)	89.7 (10.8)
Family history of diabetes (%)	20.9	20.6	35.0

Abbreviations: BMI, body mass index; kg, kilograms; m, meter; min, minutes; MOS-PF, Medical Outcomes Study-Physical Functioning; SD, standard deviation; TAFE, Technical and Further Education.

[a] Data are presented as means (SD) or percentages (%).

[b] Self-reported diabetes defined as not having physician-diagnosed diabetes nor taking diabetes medications for most of the last 4 weeks at baseline and reporting a diagnosis of diabetes between baseline and follow-up (n = 611). There were significant differences ($P < .05$) between participants with and without diabetes for all variables except for daily sitting time and country of birth.

[c] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by 2) in the past week.[17]

[d] The MOS-PF scale is a 10-item questionnaire assessing physical functioning limitations in performing daily living activities to vigorous physical activities.[13] Higher scores indicate better physical functioning.

Table 2 Unadjusted and Adjusted Odds Ratios for Incident Type 2 Diabetes by Levels of Body Mass Index, Physical Activity, and Sitting (2006–2010)

Variable	Unadjusted Odds Ratios (95% CI)	*P*-value	Adjusted Odds Ratios[a] (95% CI)	*P*-value
Body mass index category				
Normal weight (18.5 to <25 kg/m^2)	1.0 (reference)		1.0 (reference)	
Overweight (25 to <30 kg/m^2)	2.20 (1.76, 2.73)	<0.001	2.03 (1.62, 2.53)	<0.001
Obese (≥30 kg/m^2)	5.23 (4.19, 6.53)	<0.001	5.07 (4.03, 6.38)	<0.001
Physical activity[b] tertiles				
Low (0 to <300 min/week)	1.0 (reference)		1.0 (reference)	
Medium (300 to <660 min/week)	0.81 (0.67, 0.98)	0.03	0.95 (0.78, 1.15)	0.57
High (≥660 min/week)	0.74 (0.61, 0.90)	0.002	0.87 (0.71, 1.06)	0.17
Sitting time category				
Lower sitting (<8 hours/day)	1.0 (reference)		1.0 (reference)	
Higher sitting (≥8 hours/day)	0.90 (0.72, 1.13)	0.37	0.91 (0.72, 1.15)	0.42

Abbreviations: CI, confidence interval; kg, kilograms; m, meter; min, minutes.

Note. Data for n = 29,572 included in analysis, of which 611 developed diabetes. Missing covariate data (n = 275 for country of birth, n = 434 for education, n = 1 for family history of T2DM) were analyzed using a missing indicator approach.

[a] Adjusted for age group, sex, follow-up time, country of birth, education, family history of diabetes, and lifestyle risk factors (body mass index category/physical activity tertiles/sitting time category).

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by 2) in the past week.[17]

Table 3 Adjusted Odds Ratios for Associations Between Physical Activity/Sitting and Incident Type 2 Diabetes Stratified by Body Mass Index (BMI) Categories

	BMI category		
	Normal weight (18.5 to <25 kg/m^2)	Overweight (25 to <30 kg/m^2)	Obese (≥30 kg/m^2)
Variable	Adjusted Odds Ratios[a] (95% CI)	Adjusted Odds Ratios[a] (95% CI)	Adjusted Odds Ratios[a] (95% CI)
Physical activity[b] tertiles			
Low (0 to <300 min/week)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Medium (300 to <660 min/week)	1.23 (0.78, 1.94); *P* = .37	0.87 (0.64, 1.19); *P* = .38	0.92 (0.67, 1.25); *P* = .58
High (≥660 min/week)	0.80 (0.49, 1.28); *P* = .35	0.95 (0.70, 1.30); *P* = .77	0.82 (0.59, 1.15); *P* = .25
Sitting time category (%)			
Lower sitting (<8 hours/day)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Higher sitting (≥8 hours/day)	0.65 (0.33, 1.25); *P* = .20	1.02 (0.71, 1.46); *P* = .93	0.89 (0.62, 1.27); *P* = .52

Abbreviations: BMI, body mass index; CI, confidence interval; kg, kilograms; m, meter; min, minutes.

[a] Adjusted for age group, sex, follow-up time, country of birth, education, family history of diabetes and sitting time/physical activity.

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by 2) in the past week.[17]

cause and cardiovascular mortality compared with individuals with a normal BMI and poor fitness, these findings contrast with those relating to T2DM.[3] Indeed, our findings are consistent with those from a recent meta-analysis, based on prospective studies mostly including middle-aged and older adults, suggesting that BMI is a relatively more important T2DM risk factor than PA.[3] Contrary to established evidence,[22] PA was not independently associated with T2DM in the adjusted model, possibly due to measurement errors in self-reported PA, and lack of very inactive participants as references (the 45 and Up participants reported more physical activity than the general population, suggesting limited exposure variability).[23] The effect of PA could also be underestimated as BMI, which was adjusted for, may be in the causal pathway between PA and T2DM. Notwithstanding, PA remains a component of T2DM prevention interventions, as PA can contribute to weight reduction and maintenance, and can improve insulin resistance even in the absence of weight loss.

Previous studies including several prospective studies conducted in middle-aged and older adults have shown that sedentary behavior, measured mainly by television viewing time, was associated with incident T2DM.[6–9] A recent study has also found that prolonged sitting, independent of moderate-vigorous PA, is associated with incident T2DM in obese, but not normal or overweight, postmenopausal women.[10] However, our study found no association

Table 4 Adjusted Odds Ratios for Incident Type 2 Diabetes Based on Body Mass Index-Physical Activity (BMI-PA) and BMI-PA-Sitting Combinations

	Adjusted Odds Ratios					
	Model 1[a]		Model 2[b]		Model 3[c]	
Variable	Adjusted Odds Ratios (95% CI)	*P*-value	Adjusted Odds Ratios (95% CI)	*P*-value	Adjusted Odds Ratios (95% CI)	*P*-value
BMI-PA combination group[d]						
Normal weight-high PA	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA	1.39 (0.91, 2.13)	0.13	1.34 (0.87, 2.05)	0.18	1.37 (0.89, 2.10)	0.15
Normal weight-low PA	1.20 (0.75, 1.90)	0.45	1.11 (0.70, 1.76)	0.67	1.07 (0.67, 1.71)	0.77
Overweight-high PA	2.52 (1.73, 3.67)	<0.001	2.40 (1.64, 3.50)	<0.001	2.32 (1.59, 3.38)	<0.001
Overweight-med PA	2.35 (1.59, 3.45)	<0.001	2.16 (1.47, 3.19)	<0.001	2.15 (1.46, 3.18)	<0.001
Overweight-low PA	2.87 (1.97, 4.17)	<0.001	2.55 (1.75, 3.72)	<0.001	2.48 (1.70, 3.62)	<0.001
Obese-high PA	5.42 (3.61, 8.13)	<0.001	5.36 (3.57, 8.04)	<0.001	5.11 (3.40, 7.68)	<0.001
Obese-med PA	6.29 (4.24, 9.32)	<0.001	6.05 (4.08, 8.97)	<0.001	5.77 (3.89, 8.57)	<0.001
Obese-low PA	7.32 (5.07, 10.57)	<0.001	6.81 (4.70, 9.84)	<0.001	6.41 (4.42, 9.29)	<0.001
BMI-PA-sitting combination group[d]						
Normal weight-high PA-lower sitting	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA-lower sitting	1.37 (0.88, 2.12)	0.17	1.32 (0.85, 2.05)	0.22	1.34 (0.86, 2.08)	0.20
Normal weight-low PA-lower sitting	1.20 (0.74, 1.94)	0.47	1.11 (0.68, 1.80)	0.68	1.08 (0.66, 1.75)	0.77
Normal weight-high PA-higher sitting	0.29 (0.04, 2.13)	0.23	0.28 (0.04, 2.06)	0.21	0.29 (0.04, 2.09)	0.22
Normal weight-med PA-higher sitting	0.98 (0.38, 2.49)	0.96	0.92 (0.36, 2.34)	0.86	0.96 (0.38, 2.46)	0.94
Normal weight-low PA-higher sitting	0.79 (0.28, 2.22)	0.65	0.72 (0.26, 2.03)	0.54	0.70 (0.25, 1.96)	0.49
Overweight-high PA-lower sitting	2.45 (1.67, 3.60)	<0.001	2.33 (1.58, 3.43)	<0.001	2.25 (1.53, 3.31)	<0.001
Overweight-med PA-lower sitting	2.36 (1.59, 3.51)	<0.001	2.17 (1.46, 3.24)	<0.001	2.16 (1.45, 3.22)	<0.001
Overweight-low PA-lower sitting	2.46 (1.65, 3.66)	<0.001	2.18 (1.46, 3.26)	<0.001	2.11 (1.41, 3.15)	<0.001
Overweight-high PA-higher sitting	1.69 (0.71, 4.02)	0.23	1.56 (0.66, 3.71)	0.32	1.54 (0.65, 3.67)	0.33
Overweight-med PA-higher sitting	1.45 (0.67, 3.12)	0.34	1.32 (0.61, 2.84)	0.48	1.33 (0.62, 2.87)	0.47
Overweight-low PA-higher sitting	3.78 (2.24, 6.38)	<0.001	3.31 (1.95, 5.59)	<0.001	3.36 (1.99, 5.70)	<0.001
Obese-high PA-lower sitting	5.13 (3.38, 7.79)	<0.001	5.07 (3.34, 7.71)	<0.001	4.85 (3.18, 7.38)	<0.001
Obese-med PA-lower sitting	5.93 (3.92, 8.95)	<0.001	5.72 (3.78, 8.64)	<0.001	5.42 (3.58, 8.20)	<0.001
Obese-low PA-lower sitting	7.10 (4.84, 10.41)	<0.001	6.57 (4.48, 9.65)	<0.001	6.14 (4.17, 9.03)	<0.001
Obese-high PA-higher sitting	4.94 (2.06, 11.88)	<0.001	4.66 (1.94, 11.20)	0.001	4.48 (1.86, 10.81)	0.001
Obese-med PA-higher sitting	5.90 (3.11, 11.21)	<0.001	5.49 (2.88, 10.44)	<0.001	5.48 (2.88, 10.44)	<0.001
Obese-low PA-higher sitting	6.08 (3.51, 10.55)	<0.001	5.66 (3.26, 9.83)	<0.001	5.58 (3.21, 9.72)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; med, medium; PA, physical activity.

Note. Data for n = 29,572 included in analysis, of which 611 developed diabetes.

[a] Adjusted for age group only.

[b] Adjusted for age group, sex, follow-up time and BMI-PA/BMI-PA-sitting combination groups.

[c] Adjusted for age group, sex, follow-up time, country of birth, highest education, family history of diabetes and BMI-PA/BMI-PA-sitting combination groups. Missing covariate data (n = 275 for country of birth, n = 434 for education, n = 1 for family history of T2DM) were analyzed using a missing indicator approach.

[d] BMI categories defined as: normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (≥30 kg/m^2). PA categories based on PA tertiles: high (≥660 min/week), medium (300-<660 min/week) and low (0 to <300 min/week). Based on previous analysis,[20] sitting was dichotomized as higher (≥8 hours/day) and lower (<8 hours/day) sitting.

between sitting time and T2DM in the overall sample, or in any weight category. This suggests that the current evidence on sitting and T2DM is still inconclusive. As television time may not be used as a simplified marker for total sitting time, more studies on total sitting time and T2DM are needed.[11]

Strengths of this study include a large population sample, a prospective cohort design and adjustment for multiple potential confounders. Main limitations include short follow-up time, and the use of self-reported measures of lifestyle risk factors and diabetes. However, most of the study's measures have been previously validated. As individuals with healthy lifestyles were over-represented in the 45 and Up study, this study population may have limited representativeness of the general population. The sample in this study is about 2 to 3 times more active than the general population. For example, in the 2011–12 Australian Health Survey, a large, nationally representative survey of the health status of the Australian population, adults 45 years and over spent on average 205 min/week on PA (assessed using the same validated questions from the Active Australia Survey as this study).[24] However, a comparison of the 45 and Up sample with participants of the New South Wales Population Health Survey (a population representative sample) indicated similar estimates of exposure–outcome associations, although the prevalence of risk factors differed between the 2 samples.[23]

Among middle-aged and older Australian adults, BMI was a more important risk factor for T2DM than physical inactivity or prolonged sitting, and the risk associated with BMI cannot be offset by PA level nor sitting time. Nonetheless, efforts to prevent T2DM should continue to encourage healthy lifestyle behaviors such as increasing PA, as these remain important in helping to reduce overweight and obesity, and maintain a normal weight.

Acknowledgments

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4.5 CONCLUDING SUMMARY FOR THIS CHAPTER AND KNOWLEDGE GAINED FROM THIS STUDY

This was the first prospective cohort study to examine whether the increased risk of developing type 2 diabetes mellitus associated with a high body mass index could be offset by high levels of physical activity and low sitting time. Among a cohort of middle-aged and older Australians, a high body mass index was a relatively stronger risk factor for type 2 diabetes than low physical activity levels or high sitting time. When considering the joint influence of these lifestyle risk factors, high levels of physical activity and low sitting time did not attenuate the increased odds of developing type 2 diabetes that were associated with being overweight or obese. In gender-specific analyses (**Appendix 1**), findings were essentially similar to analyses in the overall sample. Further studies are needed to confirm findings from this study and to examine whether sitting time is associated with incident type 2 diabetes. Achieving and maintaining a healthy weight, by engaging in healthy lifestyle behaviours, is crucial for type 2 diabetes prevention.

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CHAPTER FIVE:
Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians

5.1 PREFACE TO THE CHAPTER

This chapter presents findings from a peer-reviewed paper that examined the separate and combined effects of six lifestyle risk factors on incident hypertension in the 45 and Up Study cohort. The lifestyle risk factors that were examined included being overweight/obese, low physical activity levels, high alcohol consumption, being a current smoker, low consumption of fruit and/or vegetables per day, and being at high risk of psychological distress. The published paper forms this chapter. It addresses specific aims #3 and #5 of this thesis as described in Chapter 1. Dissemination of this research and author contributions for this paper are described below.

5.2 RESEARCH DISSEMINATION

The research presented in this chapter has been disseminated as follows:

Published peer-reviewed paper

Nguyen B, Bauman A, Ding D. Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians. *Preventive Medicine* 2019; 118: 73-80. Available from: http://doi.org/10.1016/j.ypmed.2018.10.007 (Epub ahead of print)

Impact factor 3.434

Published abstract

Nguyen B, Bauman A, Ding D. Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians. *Revue d'Epidemiologie et de Sante Publique*. Vol 66 Suppl 5, July 2018, Pages S260-1. Available from: http://doi.org/10.1016/j.respe.2018.05.069

Conference presentations

Nguyen B, Bauman A, Ding D. Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians. *European Congress of Epidemiology*, Lyon, France, 2018. [Oral presentation]

Nguyen B, Bauman A, Ding D. Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians. *Sax Institute 45 and Up Study Collaborators' Annual Meeting,* Sydney, Australia, 2017. [Oral presentation]

Nguyen B, Bauman A, Ding D. Association between lifestyle risk factors and incident hypertension among Australians. *Australian Epidemiological Association Meeting*, Sydney, Australia, 2017. [Oral presentation]

Nguyen B, Ding D. Are lifestyle behaviours and hypertension associated among Australians? *3rd Annual Charles Perkins Centre Symposium*, Sydney, Australia, 2017. [Poster Presentation] – **Awarded best poster presentation.**

5.3 AUTHOR ATTRIBUTION STATEMENT

I, Binh Nguyen, was responsible for designing the study, analysing and interpreting data, writing drafts of the manuscript, submitting the manuscript, responding to reviewers' comments, and coordinating submission and publication of the manuscript.

My co-authors, A. Bauman and D. Ding, helped to design the study, interpret data, draft the manuscript, and revise the manuscript critically for important intellectual content.

All authors have read and approved the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.

Signature:

Dr. Ding (Melody) Ding

5.4 PAPER IN PUBLISHED FORMAT

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Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians

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ABSTRACT

This study aimed to examine the association between individual and combined lifestyle risk factors and the incidence of hypertension 1) in middle-aged and older Australians, and 2) to compare findings in men and women. A sample of 32,393 adults aged ≥45 years from New South Wales completed baseline (2006–2008) and follow-up (2010) questionnaires. Self-reported incident hypertension was defined as not having physician-diagnosed hypertension nor taking antihypertensive medications at baseline and reporting a diagnosis/treatment of hypertension at follow-up. High-risk categories for six lifestyle risk factors were defined as: a BMI ≥ 25 kg/m^2, physical activity levels < 150 min/week, consuming ≥14 alcohol drinks/week, being a current smoker, consuming < 2 fruit and/or < 3 vegetable serves/day, and being at high risk of psychological distress (Kessler-10 score ≥ 22). The association between baseline risk factors and incident hypertension was examined using logistic regression models, adjusted for socio-demographic, medical and lifestyle risk factors. After 2.7 (SD: 0.9) years of follow-up, 17.1% developed hypertension. Compared to low-risk categories, high BMI (AOR [95% CI]: 1.99 [1.85, 2.13]), high alcohol intake (1.58 [1.44, 1.73]), low physical activity levels (1.17 [1.07, 1.27]) and being a current smoker (1.15 [1.0, 1.31]) were associated with a higher incidence of hypertension in the overall sample, with similar associations in men and women. The number of high-risk lifestyle factors was positively associated with higher odds of developing hypertension in the overall sample, men and women; with a stronger association in middle-aged men. Adopting a low-risk lifestyle may prevent hypertension among middle-aged and older adults.

1. Introduction

Hypertension is the leading contributor to global disease burden (GBD 2015 Risk Factors Collaborators, 2016). It is one of the major risk factors for cardiovascular disease, which accounts for the largest number of deaths worldwide (GBD 2015 Mortality and Causes of Death Collaborators, 2016; Roth et al., 2017). As the prevalence, mortality, and disease burden of hypertension have increased considerably in the last 25 years (Forouzanfar et al., 2017), it is important to identify modifiable lifestyle risk factors that can inform strategies for hypertension and subsequent cardiovascular disease prevention.

Several lifestyle risk factors for hypertension have been identified, including being overweight or obese, an unhealthy diet, insufficient physical activity and excessive alcohol intake. A plethora of intervention (Dickinson et al., 2006; Neter et al., 2003; Xin et al., 2001) and prospective studies (Briasoulis et al., 2012; Gelber et al., 2007; Lelong et al., 2017; Liu et al., 2017) have examined these factors. Lifestyle factors tend to cluster and have synergistic health effects (Ding et al., 2015a; Krokstad et al., 2017). However, few prospective studies have investigated the combined influence of lifestyle risk factors on the development of hypertension (Cohen et al., 2012; Forman et al., 2009; Banda et al., 2010), and no study to our knowledge has compared these associations in men and women. Given the previously reported sex differences in the prevalence, control, and pathophysiology of hypertension, comparing risk factors in men and women is needed and could inform sex-specific prevention strategies (Doumas et al., 2013).

As most of the attributable global burden of blood-pressure related disease is borne by middle-aged and older people (Lawes et al., 2008), and as the prevalence of hypertension markedly increases with age (Kearney et al., 2005), it is important to examine primary prevention strategies among this age group. The aims of this study are to examine the association between individual and combined lifestyle risk factors and the incidence of hypertension 1) among a cohort of middle-aged and older Australians, and 2) separately in men and women.

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2. Methods

2.1. Study population

The baseline data were from the Sax Institute's 45 and Up Study, a prospective cohort study of 267,153 men and women aged 45 years and over, randomly sampled from the general population of New South Wales (NSW), Australia, using the Medicare database, the national universal health provider. From January 2006 to December 2008, eligible individuals joined the study by completing a postal questionnaire and providing written consent for follow-up. The study methods have been described in detail elsewhere (Banks et al., 2008). In 2010, the first 100,000 participants to join the 45 and Up Study were invited to complete the Social, Economic, and Environmental Factor (SEEF) Study follow-up questionnaire (60.4% response rate). A participant flow chart is provided in Fig. 1. Participants that reported being treated for hypertension or taking antihypertensive medication at baseline were excluded (n = 19,349). Participants that reported being treated for heart disease, high blood cholesterol, or taking medication against heart disease, high blood cholesterol or diabetes were also excluded (n = 20,982) as some of these medications may have blood pressure lowering effects and as people with diabetes commonly have high blood pressure. The final analytic sample included 32,393 participants. The 45 and Up Study was granted ethics approval by the University of NSW Human Research Ethics Committee (reference HREC 05035/HREC 10186) and the SEEF Study by the University of Sydney Human Research Ethics Committee (reference 10-2009/12187).

2.2. Measurement

The baseline and follow-up questionnaires included questions about socio-demographic characteristics, health and lifestyle factors (https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/).

2.2.1. Ascertainment of hypertension

Incident hypertension was defined, based on self-reported data, as not having physician-diagnosed hypertension nor taking antihypertensive medication at baseline and reporting either a diagnosis or treatment of hypertension at follow-up. Self-reported hypertension has been validated in similar studies involving large cohorts (Forman et al., 2009; Banda et al., 2010).

2.2.2. Baseline exposure variables

Body mass index (BMI), derived from self-reported height and weight, has been previously validated in this cohort (Ng et al., 2011). Physical activity, based on validated questions from the Active Australia Survey was calculated as the sum of time spent on walking, moderate-intensity and vigorous-intensity (weighted by two) physical activity in the past week (Australian Institute of Health and Welfare, 2003). Participants were asked about their weekly alcohol consumption as well as past and current smoking patterns. Usual daily fruit and vegetable consumption was assessed using validated short questions (Rustihauser et al., 2011). Participants' general level of psychological distress was measured using the Kessler-10 (K10) scale, a validated 10-item questionnaire about anxiety and depression symptoms experienced in the previous month (Andrews and Slade, 2001).

2.2.3. Definition of lifestyle risk categories

The six lifestyle factors described above were dichotomised as either low- or high-risk for developing hypertension. A BMI greater or equal to 25 kg/m^2, the standard World Health Organization (WHO) cut-off point for overweight, was considered high-risk. Being overweight or obese has been associated with an increased risk of developing hypertension in middle-aged men and women (Field et al., 2001). Participants who did not meet the minimal recommendation of 150 min of moderate-vigorous PA a week, as per WHO (WHO, 2010) and current Australian guidelines (Australian Department of Health, 2014), were deemed at risk. Consuming < 2 serves of fruit and/or < 3 serves of vegetables per day was defined as high-risk, based on cut-points previously used in studies involving population health surveillance (Ding et al., 2015b; Centre for Epidemiology and Research, 2008). Alcohol risk was defined as consuming > 14 drinks per week, an amount exceeding the Australian National Health and Medical Research Council's recommendations (NHMRC, 2009). Those who reported being current smokers (including daily and occasional smokers) were considered at risk. Risk of psychological distress was defined as the presence of high to very high levels of psychological distress (K10 score ≥ 22), as used in a previous study involving this cohort (Nguyen et al., 2017a).

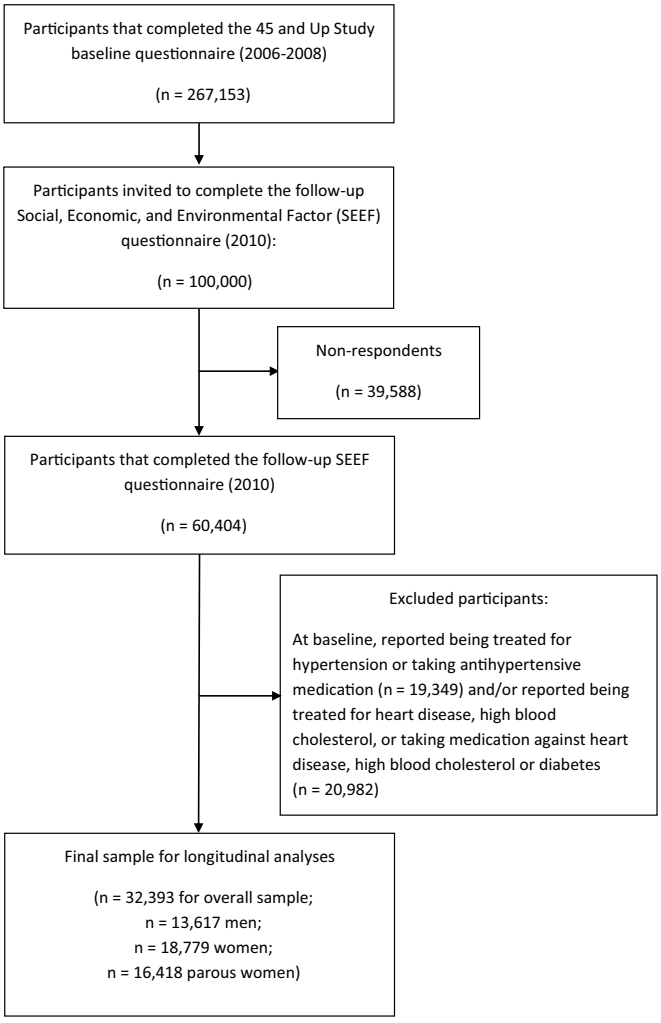

Fig. 1. Participant flow chart (45 and Up Study, 2006–2010).

To examine the combined influence of lifestyle risk factors, a lifestyle risk score (LRS) was calculated for each participant by summing up the number of lifestyle factors in the high-risk category. A combined score approach is a common approach (McAloney et al., 2013) and has been used previously by several prospective cohort studies examining associations between combined lifestyle risk factors and cardiovascular risk factors and outcomes (Banda et al., 2010; Chiuve et al., 2006; Myint et al., 2009; vanDam et al., 2008). The LRS was further categorised as: 0, 1, 2, and 3 to 6 (these scores were combined due to the small percentages of participants with 3 to 6 risk factors).

2.2.4. Covariates

Covariates were based on self-reported information from the baseline questionnaire, and included the following socio-demographic

characteristics: age (45–54, 55–64, 65–74, ≥75 years), sex, country of birth (Australia/New Zealand, Europe, Middle East, Asia, Canada/United State, Africa, other), educational attainment (university degree/higher, high school/trade apprenticeship/certificate/diploma, ≤10 years of schooling), area-level socio-economic status (quintiles based on the Socio-Economic Indexes For Area - Index of Relative Socio-Economic Disadvantage [SEIFA-IRSD; Australian Bureau of Statistics, 2008]); medical variables: family history of hypertension (yes/no), aspirin use (yes/no), omega 3 or fish oil use (yes/no); and follow-up time. In separate analyses conducted in women, additional covariates were included: oral contraceptive use (ever/never), current use of hormonal replacement therapy (yes/no), menopausal status (pre-menopausal, post-menopausal, not sure/irregular periods), and number of children given birth to (0, 1, 2, 3, ≥4). To further explore risk factors for women within the context of reproductive history, a sub-analysis involving parous women only was additionally adjusted for the following reproductive variables: mother's age for first child (years), lifetime breastfeeding duration (months), and hypertension during pregnancy (yes/no).

2.3. Statistical analysis

Baseline participant characteristics by sex were presented as means (standard deviation [SD]) or percentages. Differences in baseline characteristics between men and women were examined using student *t*-tests for continuous variables and chi-square tests for categorical variables. The association between individual lifestyle risk factors or the LRS and incident hypertension were examined using logistic regression. The lower-risk category for lifestyle factors and the LRS (LRS = 0) was chosen as the reference category. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for unadjusted and multivariate-adjusted models in the overall sample, and separately in men and women. Individual lifestyle factors were mutually adjusted for each other. We tested for effect modification by age (< 65 years vs ≥65 years) and sex by fitting interaction terms with the LRS. Finally, sensitivity analyses were conducted separately in men and women to examine whether findings differed if lifestyle factors were considered as continuous variables rather than using specific cut-points. Analyses were conducted using SPSS version 22 (IBM Corp., Armonk, NY).

3. Results

Of 32,393 participants without hypertension at baseline, 5539 (17.1%) reported hypertension at follow-up (mean [SD]: 2.7 [0.9] years). Participants' socio-demographic and lifestyle characteristics at baseline are presented in Table 1. The mean age of participants at baseline was 58.3 (SD: 9.2) years and most (80%) were born in Australia/New Zealand. More than half (58%) of the sample were women, nearly a third (30.8%) had a university degree and nearly half (46.9%) reported a family history of hypertension. More than half (53.5%) of participants were overweight/obese, more than three-quarters (83%) were physically active (≥150 min/week), and less than half (42.8%) consumed ≥2 fruit and ≥3 vegetables/day. In addition, more than three-quarters (86%) consumed ≤14 drinks of alcohol/week, nearly two-thirds (60.3%) were never smokers, less than a tenth (6.7%) were current smokers, and the majority (94.6%) had a low to moderate risk of psychological distress. Overall, more than half (53.4%) had a lower-risk lifestyle (LRS = 0–1). Compared to men, women were on average younger and had a healthier lifestyle overall, and a higher proportion of women had completed ≤10 years of education. Among women, more than half (57.3%) were post-menopausal, and on average had more than two (mean: 2.3; SD: 1.4) children. Parous women breastfed an average of 16 (SD: 16) months during their lifetime.

Table 2 shows the unadjusted and adjusted ORs for the associations between six lifestyle risk factors, the LRS, and incident hypertension in the overall sample. In unadjusted models, high-risk categories for all six lifestyle risk factors were significantly associated with higher odds of incident hypertension. After adjustment for covariates, being overweight/obese, exercising < 150 min/week, consuming > 14 drinks of alcohol/week and being a current smoker remained significantly associated with higher odds of incident hypertension. In both unadjusted and adjusted models, the odds of incident hypertension increased with an increasing number of high-risk lifestyle risk factors. Participants in the highest LRS category (LRS = 3 to 6) had 2.58 (95% CI: 2.29, 2.90) the odds of developing hypertension compared with participants without any high-risk factors.

The unadjusted and adjusted ORs for incident hypertension by categories of lifestyle risk factors and LRS are also presented separately for men (Table 3) and women (Table 4). In men, high-risk categories for BMI, physical activity, fruit and vegetable intake, alcohol intake and smoking status were associated with higher odds of incident hypertension in unadjusted models. In adjusted models, being overweight/obese, exercising < 150 min/week and consuming > 14 drinks of alcohol/week remained significant. A larger number of high-risk factors was associated with higher odds of developing hypertension following covariate adjustment.

In women, high-risk categories for BMI, physical activity, alcohol intake and current smoking status were associated with higher odds of incident hypertension in unadjusted models. Similar to findings in men, these associations remained significant for BMI, physical activity and alcohol intake following adjustment for covariates. An increasing number of high-risk factors was associated with increased odds of developing hypertension. However, the pattern of association differed significantly between men and women (test for interaction $p < 0.003$).

In unadjusted analyses, all women-specific covariates were significantly associated with incident hypertension. These associations did not remain significant following covariate adjustment. In the sub-analysis involving parous women only, lifetime breastfeeding duration and high blood pressure during pregnancy remained significantly associated with lower and higher odds of hypertension, respectively, after adjustment for additional reproductive variables.

There was a significant interaction between the LRS and age categories ($p < 0.001$). The association between the LRS and incident hypertension was stronger in individuals aged < 65 years compared to those aged ≥65 years, especially among middle-aged men (Table 5). Sensitivity analyses conducted in separately in men and women showed that results were similar when lifestyle factors were examined as continuous variables rather than using cut-points.

4. Discussion

In this study following a large cohort of middle-aged and elderly adults for three years, being overweight/obese, a high weekly alcohol intake, and a low amount of physical activity per week were associated with higher odds of developing hypertension, in both men and women. A higher number of lifestyle risk factors was associated with higher odds of incident hypertension in both the overall sample and in separate analyses in men and women. A salient finding from this study was that a higher-risk lifestyle for hypertension seemed more detrimental in middle-aged than older adults, especially in men, highlighting the importance of lifestyle risk reduction among middle-aged men.

There is growing evidence supporting the importance of considering the combined effects of lifestyle risk factors on health. To date, several prospective studies have examined associations between combined lifestyle risk factors and adverse health outcomes, such as coronary heart disease (Chiuve et al., 2006; Stampfer et al., 2000), stroke (Kurth et al., 2006; Chiuve et al., 2008; Myint et al., 2009), sudden cardiac death (Chiuve et al., 2011), myocardial infarction (Akesson et al., 2007), diabetes (Hu et al., 2001), as well as cause-specific and all-cause mortality (Ford et al., 2011; Kvaavik et al., 2010; Loef and Walach, 2012; vanDam et al., 2008). In these studies, adherence to a healthy lifestyle was generally associated with better health outcomes. To our

Table 1
Baseline characteristics[a] of participants in the overall sample (n = 32,393) and according to sex (45 and Up Study, 2006–2010).

Variable	All (n = 32,393)	Men (n = 13,614)	Women (n = 18,779)
Mean (SD) follow-up time (years)	2.7 (0.9)	2.7 (0.9)	2.7 (0.9)
Age group[b] (%)	21.9	27.8	17.6
45–54 years	43.8 (n = 14,190)	38.0 (n = 5167)	48.0 (n = 9023)
55–64 years	34.3 (n = 11,105)	34.2 (n = 4662)	34.3 (n = 6443)
65–74 years	15.5 (n = 5027)	18.8 (n = 2554)	13.2 (n = 2473)
≥75 years	6.4 (n = 2071)	9.0 (n = 1231)	4.5 (n = 840)
Country of birth[b] (%) (missing n = 315; missing n = 160 for men and missing n = 155 for women)			
Australia/New Zealand	80.0 (n = 25,677)	78.5 (n = 10,562)	81.2 (n = 15,115)
Europe	14.4 (n = 4615)	16.1 (n = 2168)	13.1 (n = 2447)
Asia	2.5 (n = 817)	2.4 (n = 320)	2.7 (n = 497)
Other	3.1 (n = 969)	3.0 (n = 404)	3.0 (n = 565)
Highest education[b] (%) (missing = 416; missing n = 185 for men and missing n = 162 for women)			
University and higher	30.8 (n = 9859)	32.0 (n = 4292)	31.0 (n = 5567)
High school/trade apprenticeship/certificate/diploma	43.2 (n = 13,846)	48.9 (n = 6562)	39.1 (n = 7284)
≤10 years	26.0 (n = 8341)	19.2 (n = 2575)	29.9 (n = 5766)
Socio-economic status (SEIFA-IRSD)[c] (%) (missing = 87; missing n = 39 for men and missing n = 48 for women)			
Lowest quintile (most disadvantaged)	13.4 (n = 4340)	13.7 (n = 1853)	13.3 (n = 2487)
Second lowest quintile	26.8 (n = 8672)	26.6 (n = 3606)	27.0 (n = 5066)
Third lowest quintile	22.3 (n = 7190)	22.5 (n = 3054)	22.1 (n = 4136)
Second highest quintile	12.1 (n = 3916)	11.9 (n = 1612)	12.3 (n = 2304)
Highest quintile (least disadvantaged)	25.3 (n = 8188)	25.4 (n = 3450)	25.3 (n = 4738)
Overweight or obese (≥25 kg/m^2)[b] (missing n = 2012; missing n = 733 for men and missing n = 1279 for women)	53.5 (n = 16,265)	62.2 (n = 8014)	47.1 (n = 8251)
Physical activity level[b,d] (%) (missing = 723; missing n = 317 for men and missing n = 406 for women)			
< 150 min/week	17.0 (n = 5387)	17.7 (n = 2350)	16.5 (n = 3037)
≥150 min/week	83.0 (n = 26,283)	82.3 (n = 10,947)	83.5 (n = 15,336)
Usually consumes ≥2 serves of fruit/day and ≥3 serves of vegetables/day[b] (%) (missing = 582; missing n = 224 for men and missing n = 48 for women)	42.8 (n = 13,607)	30.3 (n = 4056)	51.8 (n = 9551)
Usually consumes ≤14 drinks/week[b] (%) (missing = 347; missing n = 142 for men and missing n = 274 for women)	86.0 (n = 27,508)	76.1 (n = 10,257)	93.2 (n = 17,251)
Smoking status[b] (%) (missing = 14; missing n = 4 for men and missing n = 10 for women)			
Never smoker	60.3 (n = 19,520)	54.2 (n = 7378)	64.7 (n = 12,142)
Previous smoker	33.0 (n = 10,685)	38.7 (n = 5266)	28.9 (n = 5419)
Current smoker	6.7 (n = 2174)	7.1 (n = 966)	6.4 (n = 1208)
Low to moderate risk of psychological distress (K10 score < 22)[b,e] (%) (missing = 2254; missing n = 832 for men and missing n = 1422 for women)	94.6 (n = 28,521)	95.4 (n = 12,192)	94.1 (n = 16,329)
LRS[b,f] (%)			
LRS = 0	17.2 (n = 5565)	9.1 (n = 1238)	23.0 (n = 4327)
LRS = 1	36.2 (n = 11,733)	30.3 (n = 4126)	40.5 (n = 7607)
LRS = 2	30.8 (n = 9967)	37.5 (n = 5108)	25.9 (n = 4859)
LRS = 3 to 6	15.8 (n = 5128)	23.1 (n = 3142)	10.6 (n = 1986)
Family history of hypertension[b] (%) (missing = 1; missing n = 0 for men, missing n = 1 for women)	46.9 (n = 15,196)	39.1 (n = 5328)	52.6 (n = 9868)
Oral contraceptive use (%) (missing n = 212)	–	–	87.2 (n = 16,198)
Hormonal replacement therapy use (%) (missing n = 249)	–	–	34.6 (n = 6404)
Menopausal status (%) (missing = 2)	–	–	
Pre-menopausal	–	–	21.0 (n = 3941)
Post-menopausal	–	–	57.3 (n = 10,760)
Irregular periods/not sure	–	–	21.7 (n = 4076)
Number of children (missing n = 74)	–	–	2.3 (1.4) (n = 18,705)
Mother's age for first child[g] (years) (missing n = 2454)	–	–	25.5 (5.0) (n = 16,325)
Lifetime breastfeeding duration[g] (months) (missing n = 2239)	–	–	15.7 (16.0) (n = 16,540)
High blood pressure during pregnancy[g] (%)	–	–	8.1 (n = 1515)

Abbreviations: IRSD = Index of Relative Socio-economic Disadvantage, K10 = Kessler Psychological Distress Scale, LRS = lifestyle risk score, SD = standard deviation, SEIFA = Socio-Economic Indexes For Areas.

[a] Data are presented as means (SD) or percentages (%).

[b] Significantly different from men (all $p < 0.01$) based on *t*-tests for continuous variables and chi-square tests for categorical variables.

[c] A SEIFA index based on disadvantage and derived from Australian census variables including low income, low educational attainment, unemployment, and dwelling without motor vehicles (Australian Bureau of Statistics, 2008).

[d] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week (Australian Institute of Health and Welfare, 2003).

[e] The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the last four weeks (Andrews and Slade, 2001). A K10 score < 22 represents a "low-to-moderate risk" of psychological distress.

[f] Derived from the total number of lifestyle risk factors in the "high-risk" category.

[g] In parous women only (n = 16,349).

knowledge, only three studies have examined the combined influence of lifestyle risk factors on hypertension in either women (Cohen et al., 2012; Forman et al., 2009) or men (Banda et al., 2010), with findings in line with those from our study. In a large 14- (Forman et al., 2009) and 26-year (Cohen et al., 2012) prospective cohort study of women from the Nurses' Health Study, and a prospective cohort study in men followed over 10 years, having a higher number of low-risk lifestyle factors was associated with a lower risk of self-reported hypertension (Banda et al., 2010). Individual lifestyle factors examined in these studies, half of which overlapped with those considered in our study,

Table 2
Unadjusted and adjusted odds ratios for incident hypertension by categories of lifestyle risk factors in the overall sample (n = 32,393; 45 and Up Study, 2006–2010).

Variable	Unadjusted odds ratios (95% CI)	Adjusted odds ratios[a] (95% CI)
Body mass index category		
< 25 kg/m^2	1.0 (reference)	1.0 (reference)
≥ 25 kg/m^2	2.0 (1.88, 2.13)	1.99 (1.85, 2.13)
Physical activity[b] level		
≥ 150 min/week	(Reference)	1.0 (reference)
< 150 min/week	1.22 (1.13, 1.32)	1.17 (1.07, 1.27)
Usual fruit and vegetable intake		
≥ 2 serves of fruit/day and ≥ 3 serves of vegetables/day	1.0 (reference)	1.0 (reference)
< 2 serves of fruit/day and/or < 3 serves of vegetables/day	1.09 (1.03, 1.16)	1.06 (0.99, 1.13)
Alcohol intake		
≤ 14 drinks/week	1.0 (reference)	1.0 (reference)
> 14 drinks/week	1.60 (1.48, 1.73)	1.58 (1.44, 1.73)
Smoking status		
Never smoker	1.0 (reference)	1.0 (reference)
Previous smoker	1.16 (1.09, 1.24)	1.06 (0.99, 1.14)
Current smoker	1.16 (1.03, 1.30)	1.15 (1.0, 1.31)
Psychological distress (K10) score[c]		
Low to moderate risk (K10 < 22)	1.0 (reference)	1.0 (reference)
High to very high risk (K10 ≥ 22)	1.21 (1.06, 1.37)	1.15 (0.99, 1.32)
LRS[d]		
0	1.0 (reference)	1.0 (reference)
1	1.36 (1.23, 1.49)	1.35 (1.22, 1.49)
2	1.73 (1.57, 1.91)	1.76 (1.59, 1.94)
3 to 6	2.37 (2.14, 2.63)	2.45 (2.20, 2.74)

Abbreviations: CI = confidence interval, kg = kilograms, K10 = Kessler Psychological Distress Scale, LRS = lifestyle risk score, m = meter.

[a] Adjusted for age group, sex, follow-up time, country of birth, education, socio-economic status (based on Socio-Economic Indexes for Areas –Index of Relative Socio-Economic Disadvantage), family history of hypertension, omega 3 or fish oil use, aspirin use and lifestyle risk factors (body mass index, physical activity level, fruit and vegetable intake, alcohol intake, smoking status, K10 score; mutually adjusted for each other). Due to missing data, the multivariate analysis including individual lifestyle risk factors was based on n = 26,747, and the multivariate analysis including the lifestyle risk index was based on n = 31,954.

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week (Australian Institute of Health and Welfare, 2003).

[c] The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the last four weeks (Andrews and Slade, 2001). A K10 score < 22 represents a low to moderate risk of psychological distress.

[d] Derived from the total number of lifestyle risk factors in the "high-risk" category.

Table 3
Unadjusted and adjusted odds ratios for incident hypertension by categories of lifestyle risk factors in men (n = 13,614; 45 and Up Study, 2006–2010).

Variable	Unadjusted odds ratios (95% CI)	Adjusted odds ratios[a] (95% CI)
Body mass index category		
< 25 kg/m^2	1.0 (reference)	1.0 (reference)
≥ 25 kg/m^2	1.95 (1.76, 2.15)	1.97 (1.77, 2.21)
Physical activity[b] level		
≥ 150 min/week	1.0 (reference)	1.0 (reference)
< 150 min/week	1.13 (1.01, 1.26)	1.14 (1.01, 1.30)
Usual fruit and vegetable intake		
≥ 2 serves of fruit/day and ≥ 3 serves of vegetables/day	1.0 (reference)	1.0 (reference)
< 2 serves of fruit/day and/or < 3 serves of vegetables/day	1.14 (1.04, 1.26)	1.09 (0.97, 1.21)
Alcohol intake		
≤ 14 drinks/week	1.0 (reference)	1.0 (reference)
> 14 drinks/week	1.66 (1.51, 1.82)	1.62 (1.45, 1.81)
Smoking status		
Never smoker	1.0 (reference)	1.0 (reference)
Previous smoker	1.25 (1.14, 1.37)	1.08 (0.97, 1.20)
Current smoker	1.24 (1.05, 1.47)	1.16 (0.95, 1.41)
Psychological distress (K10) score[c]		
Low to moderate risk (K10 < 22)	1.0 (reference)	1.0 (reference)
High to very high risk (K10 ≥ 22)	1.22 (1.0, 1.50)	1.17 (0.94, 1.47)
LRS[d]		
0	1.0 (reference)	1.0 (reference)
1	1.19 (0.99, 1.44)	1.23 (1.02, 1.50)
2	1.60 (1.33, 1.91)	1.69 (1.40, 2.03)
3 to 6	2.39 (1.98, 2.87)	2.55 (2.10, 3.10)

Abbreviations: CI = confidence interval, kg = kilograms, K10 = Kessler Psychological Distress Scale, LRS = lifestyle risk score, m = meter.

[a] Adjusted for age group, follow-up time, country of birth, education, socio-economic status, family history of hypertension, aspirin use, omega 3 or fish oil use and lifestyle risk factors (body mass index, physical activity level, fruit and vegetable intake, alcohol intake, smoking status, K10 score; mutually adjusted for each other).

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week (Australian Institute of Health and Welfare, 2003).

[c] The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the last four weeks (Andrews and Slade, 2001). A K10 score < 22 represents a low to moderate risk of psychological distress.

[d] Derived from the total number of lifestyle risk factors in the "high-risk" category.

included BMI (Banda et al., 2010; Cohen et al., 2012; Forman et al., 2009), physical activity (Banda et al., 2010; Cohen et al., 2012; Forman et al., 2009), cardiorespiratory fitness (Banda et al., 2010), alcohol intake (Banda et al., 2010; Cohen et al., 2012; Forman et al., 2009), smoking (Banda et al., 2010), a Dietary Approach to Stop Hypertension score (Cohen et al., 2012; Forman et al., 2009), non-narcotic analgesic use (Cohen et al., 2012; Forman et al., 2009), folic acid supplementation (Forman et al., 2009) and menopause (Cohen et al., 2012). As in our study, the strongest association was observed with BMI in all of these studies (Cohen et al., 2012; Forman et al., 2009; Banda et al., 2010).

Compared to these previous studies, our study is innovative in that it examined whether poor mental health was associated with incident hypertension. Although several prospective studies have reported a link between psychological factors and the risk of hypertension, findings from previous studies have been mixed (Meng et al., 2012; Rutledge and Hogan, 2002; Shinn et al., 2001). In our study, being at high risk of psychological distress was not associated with incident hypertension. Differences in findings between studies could be due to a range of methodological factors including differences in follow-up period, sample size, exposure variables and hypertension measurement. Additional longitudinal studies may help further elucidate any relationship between psychological distress and incident hypertension.

Extending previous evidence, our study compared findings between men and women. When considered individually, BMI, alcohol intake and physical activity level were significantly associated with incident hypertension in both men and women. These findings are not surprising as it has been previously shown that BMI (Gelber et al., 2007; Shuger et al., 2008), physical activity (Liu et al., 2017) and alcohol intake (Briasoulis et al., 2012) are important individual risk factors for hypertension in both sexes. However, after adjustment for confounders, there were no apparent associations with other lifestyle risk factors in separate analyses in men and women. Although the association between being a current smoker and developing hypertension achieved significance in the overall sample, it did not remain significant in separate analyses in men and women. Whilst smoking is a known risk

Table 4
Unadjusted and adjusted odds ratios for incident hypertension by categories of lifestyle risk factors in women (n = 18,779; 45 and Up Study, 2006–2010).

Variable	Unadjusted odds ratios (95% CI)	Adjusted odds ratios[a] (95% CI)
Body mass index category		
< 25 kg/m^2	1.0 (reference)	1.0 (reference)
≥ 25 kg/m^2	2.02 (1.85, 2.21)	1.98 (1.80, 2.17)
Physical activity[b] level		
≥ 150 min/week	1.0 (reference)	1.0 (reference)
< 150 min/week	1.33 (1.19, 1.48)	1.19 (1.06, 1.34)
Usual fruit and vegetable intake		
≥ 2 serves of fruit/day and ≥ 3 serves of vegetables/day	1.0 (reference)	1.0 (reference)
< 2 serves of fruit/day and/or < 3 serves of vegetables/day	0.99 (0.91, 1.08)	1.05 (0.96, 1.15)
Alcohol intake		
≤ 14 drinks/week	1.0 (reference)	1.0 (reference)
> 14 drinks/week	1.34 (1.14, 1.57)	1.50 (1.28, 1.77)
Smoking status		
Never smoker	1.0 (reference)	1.0 (reference)
Previous smoker	1.08 (0.98, 1.18)	1.07 (0.97, 1.19)
Current smoker	1.19 (1.0, 1.40)	1.15 (0.95, 1.39)
Psychological distress (K10) score[c]		
Low to moderate risk (K10 < 22)	1.0 (reference)	1.0 (reference)
High to very high risk (K10 ≥ 22)	1.17 (0.98, 1.40)	1.08 (0.89, 1.31)
Oral contraceptive use		
No	1.0 (reference)	1.0 (reference)
Yes	0.80 (0.70, 0.90)	0.90 (0.78, 1.04)
Hormonal replacement therapy use		
No	1.0 (reference)	1.0 (reference)
Yes	1.27 (1.17, 1.39)	1.04 (0.94, 1.15)
Menopausal status		
Pre-menopausal	1.0 (reference)	1.0 (reference)
Post-menopausal	1.43 (1.28, 1.60)	1.03 (0.88, 1.19)
Irregular periods/not sure	1.39 (1.22, 1.59)	1.20 (1.03, 1.40)
Number of children	1.11 (1.07, 1.15)	1.01 (0.98, 1.04)
Mother's age for first child[e]	0.97 (0.96, 0.97)	0.99 (0.98, 1.01)
Lifetime breastfeeding duration[e]	0.99 (0.99, 0.99)	0.99 (0.99, 0.99)
High blood pressure during pregnancy[e]		
No	1.0 (reference)	1.0 (reference)
Yes	2.52 (2.24, 2.84)	2.27 (1.98, 2.61)
LRS[d]		
0	1.0 (reference)	1.0 (reference)
1	1.43 (1.27, 1.62)	1.44 (1.28, 1.62)
2	1.82 (1.60, 2.06)	1.84 (1.62, 2.08)
3 to 6	2.09 (1.79, 2.43)	2.22 (1.91, 2.58)

Abbreviations: CI = confidence interval, kg = kilograms, K10 = Kessler Psychological Distress Scale, LRS = lifestyle risk score, m = meter.

[a] Adjusted for age group, follow-up time, country of birth, education, socio-economic status, family history of hypertension, aspirin use, omega 3 or fish oil use, lifestyle risk factors (body mass index, physical activity level, fruit and vegetable intake, alcohol intake, smoking status, K10 score; mutually adjusted for each other), current use of hormonal replacement therapy, oral contraceptive use, menopausal status and number of children given birth to. Additional covariates in parous women only: mother's age for first child, lifetime breastfeeding duration and high blood pressure during pregnancy.

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week (Australian Institute of Health and Welfare, 2003).

[c] The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the last four weeks (Andrews and Slade, 2001). A K10 score < 22 represents a low to moderate risk of psychological distress.

[d] Derived from the total number of lifestyle risk factors in the "high-risk" category.

[e] In sub-analysis involving parous women only (n = 16,349).

factor for cardiovascular disease, its association with incident hypertension remains uncertain. Paradoxically, non- and previous smokers have been shown to have higher blood pressure compared to smokers (Green et al., 1986) and prolongation of smoking cessation has been associated with higher increases in blood pressure, compared with current smokers (Lee et al., 2001). The association between dietary intake and incident hypertension has been shown more consistently in previous studies (Dauchet et al., 2007; Lelong et al., 2017; Schulze et al., 2003). The lack of an association in this study could be due to self-reported intake not accurately reflecting true consumption of fruit and vegetables, as well as residual confounding from other important dietary factors such as sodium intake that could not be assessed in this study. In epidemiological studies, sodium intake is usually estimated using food frequency questionnaires. However, this method is faced with several challenges including being prone to underreporting. Although 24-hour urine collection is considered the gold standard method, but this imposes a high respondent burden in large population-based studies (McLean et al., 2017).

Gender differences were more apparent when lifestyle factors were examined in combination with the pattern of association significantly differing between men and women. A higher-risk lifestyle appeared more detrimental for developing hypertension in men than in women. In addition, our study found that the total number of lifestyle risk factors seemed more strongly associated with hypertension in middle-aged adults than older adults, especially in middle-aged men. The association in older men appeared weaker than that observed in older women. These findings concur with the well-recognised observation that there is a higher incidence of hypertension in aged-matched men compared to premenopausal women, however, after menopause, there is marked increase in women resulting in a higher incidence in women compared to men. A previous study has also found that older age attenuates the associations between several lifestyle risk factors and incident hypertension in women from the Nurses' Health Study I (Cohen et al., 2012). Physiologic changes associated with ageing, such as increased arterial stiffness, lower responsiveness of the sympathetic nervous system, and changes in sex hormones, may help to explain these findings (Cohen et al., 2012; Dubey et al., 2002). Despite a need for further studies examining potential sex differences and the moderating effects of age, these findings have important public health implications as they identify middle-aged men as a high-risk group for developing hypertension, and to a lesser extent middle-aged women, and highlight the need for prevention strategies that focus on the middle-aged population.

Middle age is a critical period for interventions as changes in blood pressure during middle age can have a significant impact on lifetime risk for cardiovascular disease. A study involving data pooled from seven epidemiologic cohort studies reported that individuals that maintain or lower their blood pressure to normal levels by 55 years of age have the lowest lifetime risk for cardiovascular disease, in comparison to those who experience an increase in blood pressure and have a higher lifetime risk for cardiovascular disease (Allen et al., 2012). Another significant finding from this study was that more than two thirds of men who developed hypertension in middle age were likely to experience a cardiovascular disease event by 85 years of age, again highlighting the importance of identifying prevention strategies for middle-aged men. Prevention efforts should also not only consider people with established hypertension but also those with lesser degrees of hypertension, as it has recently been shown that a considerable portion of cardiovascular disease burden attributable to hypertension is borne by people with pre-hypertension (Lawes et al., 2008).

Finally, a unique aspect of this study was the inclusion of a range of covariates specific to women, including those relating to reproductive history. In the sub-analysis involving parous women only, both lifetime breastfeeding duration and hypertension during pregnancy were significantly associated with incident hypertension. These findings are in agreement with previous studies. Indeed, there is emerging evidence that breastfeeding is associated with the incidence of hypertension and may offer other cardiovascular health benefits (Nguyen et al., 2017b), while high blood pressure during pregnancy has been linked to a higher

Table 5
Adjusted odds ratios for incident hypertension by categories of the lifestyle risk index stratified by sex and age (< 65 or ≥65 years; 45 and Up Study, 2006–2010).

Variable	Women (n = 18,565)		Men (n = 13,389)	
	< 65 years (n = 15,316)	≥65 years (n = 3249)	< 65 years (n = 9699)	≥65 years (n = 3690)
	AORs (95% CI)	AORs (95% CI)	AORs (95% CI)	AORs (95% CI)
LRS[a]				
0	1.0 (reference) (n = 3380)	1.0 (reference) (n = 896)	1.0 (reference) (n = 766)	1.0 (reference) (n = 445)
1	1.49 (1.30, 1.71) (n = 6147)	1.28 (1.04, 1.58) (n = 1386)	1.51 (1.15, 1.99) (n = 2749)	0.99 (0.75, 1.31) (n = 1317)
2	1.93 (1.67, 2.23) (n = 4035)	1.45 (1.15, 1.83) (n = 758)	2.17 (1.66, 2.83) (n = 3730)	1.21 (0.92, 1.60) (n = 1288)
3 to 6	2.33 (1.97, 2.75) (n = 1754)	1.51 (1.06, 2.13) (n = 209)	3.55 (2.72, 4.65) (n = 2454)	1.41 (1.04, 1.92) (n = 640)

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, kg = kilograms, K10 = Kessler Psychological Distress Scale, LRS = lifestyle risk score.
[a] Derived from the total number of lifestyle risk factors in the "high-risk" category.

risk of subsequent hypertension and cardiovascular disease (Grandi et al., 2017; Magnussent et al., 2009).

4.1. Strengths and limitations

The main strengths of this study include a large population sample, a prospective design, the use of validated measures, and a wide range of covariates considered. Sensitivity analyses were conducted with continuous variables for lifestyle risk factors. This study presents some limitations including a short follow-up time and reliance on self-reported data, which may introduce bias. However, hypertension and lifestyle risk factors were assessed using mostly validated measures. The possibility of residual confounding could not be excluded despite the inclusion of multiple covariates. For example, important dietary factors such as sodium intake could not be assessed from the limited number of short dietary questions. While it is possible that this study sample may not be representative of the general population, a previous study comparing 45 and Up Study participants to participants from a representative NSW Population Health Survey reported similar estimates for exposure-outcome associations, despite different risk factor prevalence (Mealing et al., 2010). The minimal information available about SEEF non-respondents may affect the generalisability of findings.

5. Conclusion

Findings from this study are of public health significance as hypertension is one of the most important preventable causes of premature deaths worldwide. Results from this study highlight the importance of adopting an overall healthy lifestyle, particularly in middle-aged men who were identified as a higher risk group. The reduction of lifestyle risk factors is an essential component of prevention strategies aimed at reducing the incidence of hypertension and preventing subsequent cardiovascular disease.

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Conflicts of interest

None declared.

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5.5 CONCLUDING SUMMARY FOR THIS CHAPTER AND KNOWLEDGE GAINED FROM THIS STUDY

To our knowledge, this was the first prospective cohort study to compare associations between lifestyle risk factors and incident hypertension in men and women. Being overweight/obese, high alcohol intake, low physical activity levels and being a current smoker were significantly associated with a higher incidence of hypertension. There was no clear association between being at high risk of psychological distress and incident hypertension. When lifestyle risk factors were examined jointly, a higher number of lifestyle risk factors was associated with higher odds of developing hypertension. Findings were similar in men and women in relation to individual lifestyle risk factors, with the exception that smoking was not significantly associated with incident hypertension in gender-based analyses. In women, breastfeeding was shown to be protective. The association between the number of lifestyle risk factors and incident hypertension was stronger in middle-aged adults than older adults, particularly in middle-aged men. Further research is needed to examine whether middle-aged men are indeed a higher risk group and whether psychological distress is associated with incident hypertension.

CHAPTER SIX:
Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review

6.1 PREFACE TO THE CHAPTER

This chapter presents findings from a systematic review that examined the association between breastfeeding and maternal cardiovascular risk factors and outcomes, including metabolic syndrome, hypertension and CVD. The published, peer-reviewed paper addresses specific aim #4 of this thesis as described in Chapter 1. Supplementary material included as part of this published paper is also presented in this chapter. Dissemination of this research and author contributions for this paper are described below.

6.2 RESEARCH DISSEMINATION

The research presented in this chapter has been disseminated as follows:

Published peer-reviewed paper

Nguyen B, Jin K, Ding D. Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review. *PLoS ONE* 2017; 12(11): e0187923.

Impact factor 2.766

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Nguyen B, Jin K, Ding D. Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review. *The International Society for Behavioral Nutrition and Physical Activity Annual Meeting*, Victoria, Canada, 2017. [Poster presentation]

6.3 AUTHOR ATTRIBUTION STATEMENT

I, Binh Nguyen, was responsible for designing the study, analysing and interpreting data, writing drafts of the manuscript, submitting the manuscript, responding to reviewers' comments, and coordinating submission and publication of the manuscript.

My co-authors, K. Jin and D. Ding, helped to design the study, analyse and interpret data, draft and revise the manuscript critically for important intellectual content.

All authors have read and approved the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.

Signature:

Dr. Ding (Melody) Ding

6.4 PAPER IN PUBLISHED FORMAT FOLLOWED BY CORRESPONDING SUPPLEMENTARY MATERIAL

PLOS ONE

RESEARCH ARTICLE

Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review

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Abstract

Background

There is growing evidence that breastfeeding has short- and long-term cardiovascular health benefits for mothers. The objectives of this systematic review were to examine the association between breastfeeding and maternal cardiovascular risk factors and outcomes that have not previously been synthesized systematically, including metabolic syndrome, hypertension and cardiovascular disease.

Methods and findings

This systematic review meets PRISMA guidelines. The MEDLINE, EMBASE and CINAHL databases were systematically searched for relevant publications of any study design from the earliest publication date to March 2016. The reference lists from selected articles were reviewed, and forward and backward referencing were conducted. The methodological quality of reviewed articles was appraised using validated checklists.

Twenty-one studies meeting the inclusion criteria examined the association between self-reported breastfeeding and one or more of the following outcomes: metabolic syndrome/metabolic risk factors (n = 10), inflammatory markers/adipokines (n = 2), hypertension (n = 7), subclinical cardiovascular disease (n = 2), prevalence/incidence of cardiovascular disease (n = 3) and cardiovascular disease mortality (n = 2). Overall, 19 studies (10 cross-sectional/retrospective, 9 prospective) reported significant protective effects of breastfeeding, nine studies (3 cross-sectional/retrospective, 5 prospective, 1 cluster randomized controlled trial) reported non-significant findings and none reported detrimental effects of breastfeeding. In most studies reporting significant associations, breastfeeding remained associated with both short- and long-term maternal cardiovascular health risk factors/outcomes, even after covariate adjustment. Findings from several studies suggested that the effects of breastfeeding may diminish with age and a dose-response association between breastfeeding and several metabolic risk factors. However, further longitudinal studies, including studies that measure exclusive breastfeeding, are needed to confirm these findings.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

The evidence from this review suggests that breastfeeding is associated with cardiovascular health benefits. However, results should be interpreted with caution as the evidence gathered for each individual outcome was limited by the small number of observational studies. Additional prospective studies are needed.

PROSPERO registration number

CRD42016047766.

Introduction

Cardiovascular disease is the leading cause of death among women globally [1] and lifestyle-related factors play a key role in its prevention. Considerable attention has been given to more conventional risk factors such as obesity, physical inactivity and an unhealthy diet. However, other modifiable behaviours, such as breastfeeding, should be considered and incorporated in the development of potential strategies to prevent cardiovascular disease.

While the importance of breastfeeding is well recognized for infant and child health, there is growing interest in maternal health outcomes. Breastfeeding has favourable short-term effects on maternal metabolic health, including lipid homeostasis [2–4], glucose homeostasis and insulin sensitivity [5,6]. Evidence from observational studies is accumulating for an association between breastfeeding and longer-term maternal cardiovascular risk factors such as hypertension [7,8], type 2 diabetes [9,10], obesity [11], and metabolic syndrome [MS] [12]. Breastfeeding has also been linked to cardiovascular disease incidence [13] and mortality [14].

To date, there have been several systematic reviews examining the association between breastfeeding and cardiovascular risk factors such as postpartum weight change, body composition and type 2 diabetes [15–18]. Findings from these reviews suggest that breastfeeding may be associated with a reduced risk of type 2 diabetes [16,18] while the associations with postpartum weight change and body composition are unclear [15,17,18]. To our knowledge, the evidence for an association between breastfeeding and other cardiovascular risk factors and outcomes such as MS, hypertension and cardiovascular disease, has not been systematically summarized. With growing evidence suggesting that breastfeeding has both short- and long-term effects on maternal cardiovascular health outcomes, it is important to evaluate whether breastfeeding can be a modifiable risk factor for cardiovascular disease in parous women and whether lactation has long-term beneficial effects for maternal cardiovascular health.

Therefore, the objectives of this systematic review were to summarize the relationship of breastfeeding with maternal cardiovascular risk factors and outcomes that have not previously been reviewed systematically and to synthesize the findings that have been recently evaluated systematically. Reviewing this evidence systematically can provide valuable information for future guidelines and strategies for cardiovascular disease prevention.

Methods

Details of the protocol for this systematic review were registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42016047766) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016047766. This systematic review meets Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (S1 Checklist) [19].

Search strategy

The electronic databases MEDLINE, EMBASE and CINAHL were searched for relevant publications, from the earliest publication date to March 2016, using multiple subject headings and text words in combination (S1 Table). Additional articles were identified through backward and forward reference searching. Authors of published conference abstracts were contacted to identify any corresponding full text publications. Only full text publications of studies on humans and published in English were considered.

Inclusion criteria and study selection

Articles of any study design (e.g. cross-sectional/retrospective, prospective cohort, cluster randomized controlled trial [RCT]) were included in this systematic review if they investigated the association of breastfeeding with any maternal cardiovascular risk factor and/or cardiovascular outcome of a biological nature. Possible cardiovascular risk factors included: weight change, body mass index (BMI), waist circumference, body composition (e.g. visceral adiposity), hypertension, type 2 diabetes mellitus, hyperlipidemia, MS/risk factors and inflammatory markers. Studies on lifestyle risk factors, such as smoking, physical inactivity and an unhealthy diet, were not considered. Cardiovascular outcomes included subclinical and clinical cardiovascular disease prevalence, incidence and mortality. All study time periods, definitions of breastfeeding (whether exclusive or complemented by other foods) and studies that involved women with any menopausal status were accepted. Studies were excluded if they had a small sample size (defined arbitrarily as $<$100 participants) and if they examined risk factors/outcomes relating only to: the breastfed child, cancer, and pregnancy complications (e.g. gestational diabetes mellitus, pre-eclampsia and pre-term delivery). Two reviewers (BN and KJ) independently screened the titles and abstracts of retrieved articles to assess study eligibility. Any disagreement or uncertainty was resolved through discussion. The same reviewers reviewed the full text articles that met the inclusion criteria or with uncertain eligibility. Any disagreement was resolved by consensus. Although systematic reviews were not included among the selected studies, recent systematic reviews were identified and summarized for several outcomes of interest (postpartum weight change, body composition and type 2 diabetes) [15–18]. Studies involving maternal outcomes of interest that had not been previously systematically assessed were reviewed (MS/metabolic risk factors, hypertension, inflammatory markers, adipokines, subclinical cardiovascular disease, and cardiovascular disease prevalence, incidence and mortality).

Quality assessment and data extraction

One reviewer (BN) assessed the methodological quality of cross-sectional/retrospective and prospective cohort studies by using an adapted 15-item checklist derived from checklists for the reporting of observational studies (S2 Table) [20]. The single cluster RCT trial was appraised against a quality assessment checklist based on a tool developed by the Cochrane collaboration for assessing risk of bias in randomized studies [21] and relating to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, accurate outcome reporting and other sources of bias addressed. For each study, an overall study quality rating was allocated based on the total number of individual criteria met or addressed. Studies were rated as: "low quality" if $\leq$1/3 of individual criteria were met, "medium quality" if $>$1/3-$\leq$2/3 of individual criteria were met and "high quality" if $>$2/3 of criteria were met. Five articles (~25%) were randomly selected from the included studies and independently appraised by the

second reviewer (KJ). The overall agreement rate between both authors for the quality rating of these five articles was 100%.

The following data were extracted from each article: study design, country in which the study was conducted, cohort/study designation, sample size, brief participant description, age range, mean follow-up or period, type of outcome measure(s), breastfeeding comparison categories, effect sizes (most commonly reported as odds ratios or relative risks with 95% confidence intervals) and covariates adjusted for. The expected direction of each association was hypothesized based on existing literature and coded as: + (significant association in the hypothesized direction),–(significant association not in the hypothesized direction), 0 (non-significant association). Due to the heterogeneous nature of the studies and limited number of studies for each outcome of interest, only a qualitative analysis of included studies was conducted.

Breastfeeding terms and categories

In this review, the terms breastfeeding and lactation are used interchangeably. Breastfeeding was self-reported in all included studies. Lactation history refers to any reported history (usually $\geq$1 month) of breastfeeding (ever vs. never). Lactation duration is the reported length of time a woman breastfed a child. Exclusive lactation duration is the length of time a woman exclusively breastfed a child before introducing complementary foods. Lifetime lactation duration is the cumulative amount of time a woman reportedly breastfed across all pregnancies and average lactation duration is the average amount of time a woman breastfed each child.

Results

Selection of studies

The study selection process is shown in Fig 1. The literature searches yielded 581 unique citations, of which 37 were identified as potentially relevant. Following full text review, 16 studies were excluded based on small sample size or if they related to outcomes of interest that had been recently reviewed in retrieved systematic reviews (i.e., adiposity, body composition, and type 2 diabetes). Twenty-one articles examining the association between breastfeeding and one or more of the following outcomes were included for review: MS/metabolic risk factors (n = 10), hypertension (n = 7), inflammatory markers/adipokines (n = 2), subclinical cardiovascular disease (n = 2), prevalence/incidence of cardiovascular disease (n = 3) and cardiovascular disease mortality (n = 2).

Critical appraisal

Out of 21 included papers, 16 (76%) were rated as high quality and 5 (24%) as medium quality (S3 and S4 Tables). Although most quality assessment criteria were adequately addressed, many observational studies failed to describe the reliability (n = 15) and/or validity (n = 12) of the breastfeeding measure and the number of participants with missing data for the exposure/outcome of interest (n = 6).

Study characteristics

Tables 1–5 provide details of reviewed studies. Nearly all papers (95%) were published in the last decade. Of the 21 included studies, 9 were cross-sectional/retrospective [22–30], 10 were prospective [7,8,12–14,31–35], 1 reported both cross-sectional/retrospective and prospective data [36], and 1 was a cluster RCT [37]. More than half of the studies were conducted in the United States (US) (n = 11), with the remaining conducted in Europe (n = 4), Asia (n = 5), and

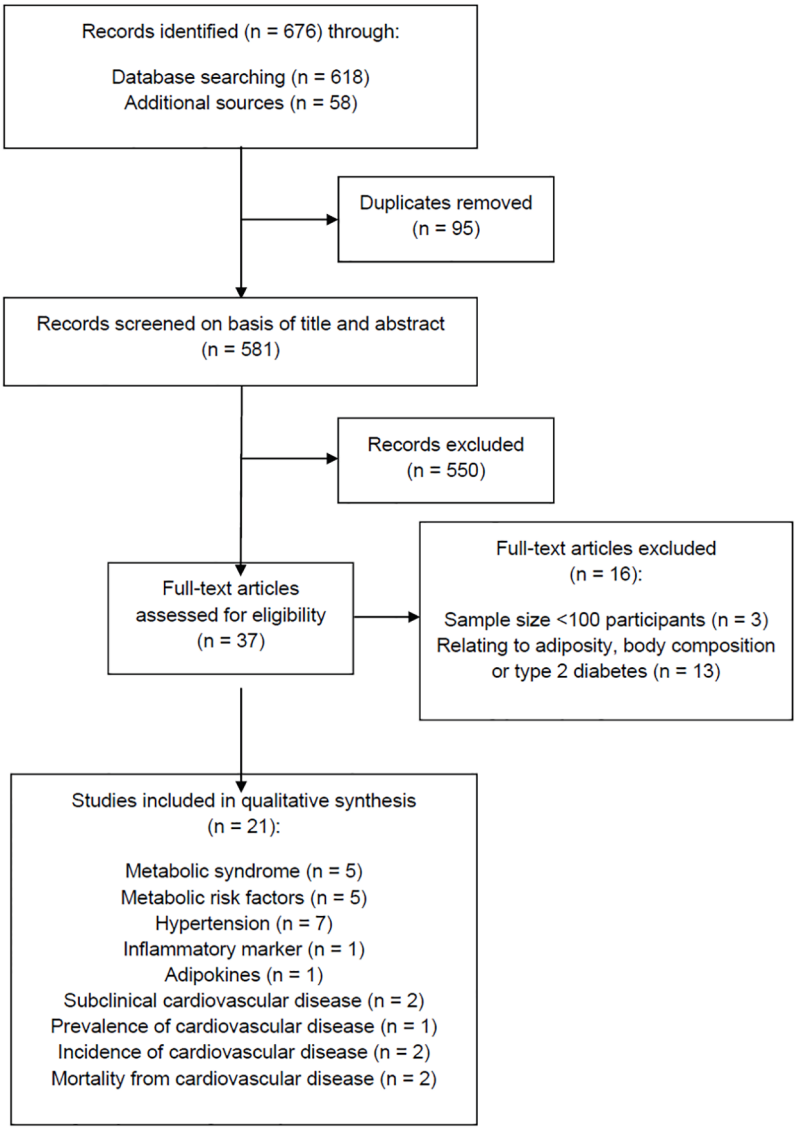

Fig 1. Selection of articles for systematic review.

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Australia (n = 1). Sample sizes ranged from 297 to 267,400 participants (median = 6,914) and the age of participants varied between 18 and 89 years of age. In prospective studies, participants were followed up between 3 and 20 years. Breastfeeding was assessed mainly by self-administered questionnaires (16/21 studies) and also by interviewer-administered questionnaires (6/21 studies). Study outcomes were mostly measured, although several were self-reported.

Association between breastfeeding and maternal cardiovascular risk factors and outcomes

Weight change/body composition. A 2014 systematic review by Neville et al., based on 37 prospective studies and eight retrospective studies, assessed the relationship between breastfeeding and changes in postpartum weight or body composition in mothers ≤2 years

Table 1. Summary of included studies with metabolic syndrome as the outcome.

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Cross-sectional/retrospective studies							
Cho et al. (2009) [24]	Korea, Korean National Health and Nutrition Examination Survey	892 post-menopausal women; 43–89 years	N/A	Measured; Prevalent MS	Ever (≥1 month) vs. never	1.20 (0.65, 2.20)	Age, marital status, SES, smoking, alcohol, PA, BMI
Ram et al. (2008) [22]	US, Study of Women's Health Across the Nation (SWAN)	2,516 parous, pre-menopausal women; 42–52 years	N/A	Measured; Prevalent MS	Ever vs. never Per year lifetime	0.77 (0.62, 0.96) 0.88 (0.77, 0.99)	Study site, age, ethnicity, SES, smoking, PA, caloric intake, high school BMI, parity
Cohen et al. (2006) [23]	US, Third National Health and Nutrition Examination Survey (NHANES III)	4,699 non-pregnant, parous women; ≥20 years	N/A	Measured; Prevalent MS	Ever (≥1 month) vs. never	1.02 (0.78, 1.34)	Age, ethnicity, SES, smoking, alcohol, PA, BMI, OC, HRT
Prospective studies							
Ramezani Tehrani et al. (2014) [31]	Iran, Tehran Lipid and Glucose Study (TLGS)	925 women without prevalent MS at baseline; 15–50 years at baseline	9	Measured; Incident MS	Lifetime lactation duration; Never 1–6 months 7–12 months 13–23 months ≥24 months	 1.5 (0.7, 3.0) 1.8 (0.7, 4.1) 1.5 (0.7, 3.2) 1.8 (1.0, 3.4) Reference	Age, PA, caloric intake, BMI, parity
Gunderson et al. (2010) [12]	US, Coronary Artery Risk Development in Young Adults (CARDIA) Study	620 nulliparous women without prevalent MS at baseline; delivered ≥1 singleton live birth during the follow-up period; 18–30 years at baseline	20	Measured; Incident MS	Lifetime lactation duration; 0–1 month >1–5 months 6–9 months >9 months P-trend	 Reference 0.61 (0.36, 1.05) 0.52 (0.29, 0.93) 0.44 (0.23, 0.84) 0.03	Study centre, age, ethnicity, SES, smoking, PA, BMI, MS components[b], parity

Abbreviations: BMI = body mass index, CI = confidence interval, HRT = hormonal replacement therapy, MS = Metabolic Syndrome, N/A = not applicable, OC = oral contraceptives, OR = odds ratio, PA = physical activity, RR = relative risk, SES = socioeconomic status, US = United States.

[a] For the assessment of breastfeeding, self-reported measures included lactation history: defined as ever breastfeeding; lactation duration: length of time a woman breastfed a child; exclusive lactation duration: length of time a woman exclusively breastfed a child before introducing complementary foods; lifetime lactation duration: cumulative amount of time a woman breastfed across all pregnancies and average lactation duration: lifetime lactation duration divided by the total number of children. For lactation history, the reference category is the second category mentioned (e.g. for ever vs. never, never is the reference category).

[b] For this study, MS components related to waist circumference measure, fasting triglyceride levels, high-density lipoprotein cholesterol levels, systolic or diastolic blood pressure or treatment with antihypertensive medication, and fasting glucose levels or treatment with diabetes medication.

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postpartum [17]. Most studies found little or no association between breastfeeding and either change in postpartum weight or maternal body composition.

In 2015, a systematic review conducted by Chowdury et al. [15] updated the review on postpartum weight change by Neville et al. [17] with five additional studies. The authors concluded that there were no clear associations between breastfeeding and postpartum weight change,

Table 2. Summary of included studies with metabolic risk factors as the outcome.

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Cross-sectional studies							
Henriques et al. (2015)[b] [25]	Portugal, Birth cohort generation XXI	1,847 mothers from public hospital maternity clinics; normal BMI: mean age (SD) = 34.4 (5.2); overweight BMI: mean age (SD) = 35.2 (5.2); obese BMI: mean age (SD): 35.3 (5.3)	N/A Assessed 4 years postpar-tum	Healthy metabolic phenotype (outcomes measured or self-reported medications) defined as the absence of HT, diabetes, dyslipidemia, CRP≤3mg/L and <2nd tertile of HOMA-IR	Lactation duration; Normal BMI Ow metab healthy: Never ≤26 weeks >26 weeks Ow metab not healthy: Never ≤26 weeks >26 weeks Ob metab healthy: Never ≤26 weeks >26 weeks Ob metab not healthy: Never ≤26 weeks >26 weeks	Reference Reference 0.84 (0.39, 1.82) 1.10 (0.50, 2.40) Reference 0.58 (0.33, 1.00) 0.64 (0.37, 1.12) Reference 0.65 (0.18, 2.33) 0.85 (0.23, 3.08) Reference 0.44 (0.26, 0.74) 0.39 (0.23, 0.68)	Age, family history of CVD/cardiometabolic risk factors, PA, OC
Natland et al. (2012) [26] ≤50 years	Norway, Nord-Trøndelag Health Survey (HUNT2)	21,368 non-pregnant, parous women without prevalent MI, stroke, angina pectoris or diabetes prior to the first birth; not currently/ previously taking anti-hypertensive medication for BP data analysis; and with TG levels <4.5 mmol/L for LDL-C analyses; 20–85 years	N/A	Measured; metabolic risk factors WC; non-fasting: serum levels of TG, total chol, HDL-C, LDL-C and blood glucose	Lifetime lactation duration; Never 1–6 months 7–12 months 13–23 months ≥24 months	Lifetime lactation duration was inversely associated with WC, TG, total chol, LDL-C, and HDL-C (all P-trends<0.001 except for HDL-C P-trend = 0.008). P-trend for blood glucose was not significant. The estimates were attenuated after further adjustment for BMI (for all lipids; no association remained for HDL-C) but remained similar after adjustment for time since last birth.	Age, marital status, SES, smoking, PA, time since last meal (for serum lipids and blood glucose), parity
Natland et al. (2012) [26] >50 years	-	-	-	-	-	Significant association with WC only (p-trend = 0.03)	-
Schwarz et al. (2009) [36]	US, Women's Health Initiative (WHI)	139,681 parous, postmenopau-sal women with ≥1 live birth; 50–79 years	N/A	Measured and/or self-reported (use of chol-lowering medication) hyperlipidemia	Lifetime lactation duration: Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend Never ≥12 months	 Reference 0.93 (0.89, 0.97) 0.88 (0.83, 0.94) 0.81 (0.76, 0.87) 0.80 (0.73, 0.87) <0.0001 Reference 0.81, p<0.001	Age, ethnicity, SES, family history of diabetes/MI/ stroke, smoking, PA, dietary intake, use of aspirin/ multivitamin, BMI, parity, HRT

(*Continued*)

Table 2. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Prospective studies							
Stuebe et al. (2010) [33]	US, Project Viva	570 women with a singleton pregnancy; <22 weeks gestation at baseline; mean age (SD) at 3 years postpartum: no lactation: 36.0 (4.8); >0–<3 months lactation: 36.8 (6.0); 3–<6 months: 37.2 (5.3); 6–<12 months: 38.2 (4.6); ≥12 months: 38.8 (5.0)	3 years postpar-tum	Measured; BMI, WC and metabolic markers: HbA1c, SHBG, fasting insulin, glucose, HOMA-IR, total chol, LDL-C, HDL-C, TG 175 subjects had fasting blood samples	Lactation duration: Never >0-<3 months 3-<6 months 6-<12 months ≥12 months Exclusive lactation duration: Never >0-<1 months 1-<3 months 3-<6 months ≥6 months	No significant associations between either lactation duration or exclusive lactation duration and outcome measures. Adjustment for BMI before pregnancy eliminated all unadjusted associations with HOMA_IR, fasting insulin, SHBG and 3-year postpartum WC.	Family history of type 2 diabetes, smoking, PA, dietary intake, intention to lose weight, self-reported weight at 12 months, pre-pregnancy BMI, gestational weight gain, gestational glucose tolerance, parity, OC
Gunderson et al. (2007) [32]	US, Coronary Artery Risk Develop-ment in Young Adults (CARDIA) Study	1,051 non-pregnant women or who delivered 1 singleton live birth during the 3-year interval, without prevalent MS at baseline; 24–42 years at baseline (year 7)	3 (interval between years 7–10 follow-up)	Measured; mean change in metabolic risk factors: fasting plasma glucose, insulin, HOMA-IR, LDL-C, total chol, HDL-C, TG, BP, weight, WC	Non-pregnant, no lactation, and lactated and weaned (post-weaning) groups. Post-weaning group also dichotomised based on lactation duration: <3 and ≥3 months	Both the no lactation and post-weaning groups had greater adjusted mean gains in WC and decrements in HDL-C than non-pregnant women (all p<0.001). LDL-C (p<0.05) and fasting insulin (p = 0.06) increased more for the no lactation group compared to the other two groups. ≥3 months lactation was associated with a smaller decrement in HDL-C than <3 months (p<0.01).	Baseline age, ethnicity, SES, smoking, BMI, time since weaning to year 10 examination (for analyses within post-weaning group only), parity, OC

Abbreviations: BMI = body mass index, BP = blood pressure, chol = cholesterol, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, HRT = hormonal replacement therapy, HT = hypertension, LDL-C = low-density lipoprotein cholesterol, metab = metabolically, MI = myocardial infarction, N/A = not applicable, Ob = obese, OC = oral contraceptives, OR = Odds Ratio, Ow = overweight, PA = physical activity, RR = relative risk, SD = standard deviation, SES = socioeconomic status, SHBG = sex hormone-binding globulin, TG = triglycerides, US = United States, WC = waist circumference.

[a] For the assessment of breastfeeding, self-reported measures included lactation history: defined as ever breastfeeding; lactation duration: length of time a woman breastfed a child; exclusive lactation duration: length of time a woman exclusively breastfed a child before introducing complementary foods; lifetime lactation duration: cumulative amount of time a woman breastfed across all pregnancies and average lactation duration: lifetime lactation duration divided by the total number of children. For lactation history, the reference category is the second category mentioned (e.g. for ever vs. never, never is the reference category).

[b] In this study, women who breastfed their child >26 weeks were less likely to be obese and "metabolically unhealthy" (defined as the presence of HT, diabetes, dyslipidemia, CRP>3mg/L and >2nd tertile of HOMA-IR).

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Table 3. Summary of included studies with hypertension as the outcome.

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Cross-sectional/retrospective studies							
Zhang et al. (2015) [27]	China	9,128 parous women with only one lifetime birth; 40–81 years	N/A	Measured or self-reported (previous physician diagnosis of HT or current use of anti-hypertensive medication) HT	Never vs. ever P-trend Lactation duration; Never >0–6 months >6–12 months >12 months P-trend	1.18 (1.05, 1.32) 0.01 Reference 0.87 (0.76, 0.99) 0.83 (0.68, 1.0) 0.79 (0.65, 0.97) 0.04	Age, SES, family history of HT, smoking, alcohol, BMI, postpartum BMI, WHR, age of menarche, age of child-bearing, menopausal status, OC
Lupton et al. (2013) [28]	Australia, 45 and Up Study	74,785 women who had never given birth or who gave birth between 18–45 years of age and who were not diagnosed with HT during pregnancy; ≥45 years	N/A	Self-reported HT (having been treated in the last month)	Nulliparous Parous, never Parous, ever	Reference 1.06 (0.95–1.18)[b] 0.89 (0.82–0.97)[b]	Age, country of origin, SES, family history of HT, smoking, alcohol, PA, BMI, OC, HRT
Lupton et al. (2013) [28] 45-<54 years	-	-	-	-	Lifetime lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months 18->24 months ≥24 months Average lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months ≥18 months	 Reference 0.88 (0.63, 1.24)[b] 0.87 (0.62, 1.20)[b] 0.74 (0.55, 0.98)[b] 0.71 (0.53, 0.95)[b] 0.57 (0.41, 0.79)[b] 0.58 (0.44, 0.77)[b] Reference 0.87 (0.66, 1.16)[b] 0.76 (0.57, 1.0)[b] 0.61 (0.47, 0.80)[b] 0.60 (0.44, 0.81)[b] 0.62 (0.42, 0.91)[b]	-
Lupton et al. (2013) [28] 54-<64 years	-	-	-	-	Lifetime lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months 18->24 months ≥24 months Average lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months ≥18 months	 Reference 0.97 (0.78, 1.20)[b] 0.84 (0.69, 1.02)[b] 0.81 (0.68, 0.96)[b] 0.78 (0.64, 0.94)[b] 0.71 (0.57, 0.89)[b] 0.60 (0.50, 0.73)[b] Reference 0.90 (0.76, 1.06)[b] 0.81 (0.69, 0.97)[b] 0.71 (0.60, 0.84)[b] 0.64 (0.51, 0.81)[b] 0.54 (0.39, 0.76)[b]	-

(*Continued*)

Table 3. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Lupton et al. (2013) [28] ≥64 years	-	-	-	-	Lifetime lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months 18->24 months ≥24 months Average lactation duration; Parous, never 1-<3 months 3-<6 months 6-<12 months 12-<18 months ≥18 months	 Reference 1.08 (0.89, 1.31)[b] 1.11 (0.94, 1.31)[b] 1.04 (0.90, 1.20)[b] 1.06 (0.91, 1.24)[b] 1.07 (0.90, 1.28)[b] 1.03 (0.88, 1.22)[b] Reference 1.06 (0.92, 1.22)[b] 1.04 (0.91, 1.20)[b] 1.12 (0.97, 1.29)[b] 0.87 (0.65, 1.18)[b] 0.36 (0.17, 0.84)[b]	-
Natland et al. (2012) [26] ≤50 years	Norway, Nord-Trøndelag Health Survey (HUNT2)	21,368 non-pregnant, parous women without prevalent MI, stroke, angina pectoris or diabetes prior to the first birth; not currently/ previously taking anti-hypertensive medication; 20–85 years	N/A	Measured or self-reported (current use of anti-hypertensive medication) HT	Lifetime lactation duration; Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend	 1.88 (1.41, 2.51) 1.24 (1.03, 1.49) 1.16 (0.98, 1.37) 1.03 (0.88, 1.21) Reference <0.001 The estimates were attenuated after adjustment for BMI and time since last birth.	Age, marital status, SES, smoking, PA, time since last meal (for serum lipids and blood glucose), parity
Natland et al. (2012) [26] >50 years	-	-	-	-	Lifetime lactation duration; Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend	 1.26 (0.96, 1.65) 0.88 (0.75, 1.02) 0.93 (0.80, 1.07) 0.89 (0.78, 1.01) Reference 0.944	
Schwarz et al. (2009) [36]	US, Women's Health Initiative (WHI)	139,681 postmenopau-sal women with ≥1 live birth; 50–79 years	N/A	Measured or self-reported (history of treated HT) HT	Lifetime lactation duration: Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend Never ≥12 months	 Reference 0.95 (0.92, 0.98) 0.88 (0.84, 0.92) 0.89 (0.84, 0.93) 0.87 (0.82, 0.93) <0.0001 Reference 0.88, p<0.001	Age, ethnicity, SES, family history of diabetes/MI/ stroke, smoking, PA, dietary intake, use of aspirin/ multivitamin, BMI, parity, HRT
Prospective studies							

(*Continued*)

Table 3. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Stuebe et al. (2011) [7]	US, US Nurses' Health Study II	55,636 parous women without prevalent HT, diabetes, CVD, hyperlipidemia or cancer at baseline; 25–42 years at baseline	1991–2005	Self-reported; incidence of HT (previously diagnosed by a physician excluding during pregnancy)	Lactation duration for the first child: Never >0–3 months >3-<6 months 6-<9 months 9-<12 months ≥12 months P-trend Exclusive lactation duration: Never Breastfed, never exclusively >0–3 months >3-<6 months ≥6 months P-trend Average lactation duration: Never >0–3 months >3-<6 months 6-<9 months 9-<12 months ≥12 months P-trend Average exclusive lactation duration: Never Breastfed, never exclusively >0–3 months >3-<6 months ≥6 months P-trend	 1.27 (1.18, 1.36) 1.29 (1.20, 1.39) 1.16 (1.08, 1.25) 1.11 (1.03, 1.19) 1.03 (0.95, 1.11) Reference <0.001 1.29 (1.20, 1.39) 1.11 (1.03, 1.19) 1.08 (0.99, 1.18) 1.03 (0.95, 1.12) Reference <0.001 1.22 (1.13, 1.32) 1.21 (1.12, 1.30) 1.19 (1.11, 1.28) 1.09 (1.02, 1.18) 1.07 (0.99, 1.17) Reference <0.001 1.16 (1.05, 1.27) 1.14 (1.04, 1.24) 1.08 (0.99, 1.18) 1.04 (0.95, 1.13) Reference <0.001	Race, family history of HT, history of pregnancy complications, smoking, alcohol, vigorous PA, DASH diet score quintile, BMI at age 18 years, nonnarcotic analgesic use, year of first birth, OC
Lee et al. (2005) [8]	Korea, Korean Women's Cohort (KWC) Study	177,749 pre-menopausal women without prevalent HT at baseline; 20–59 years at baseline	6	Measured or self-reported (current use of anti-hypertensive medication) HT	Ever vs. never Lifetime lactation duration: Never 1–6 months 7–12 months 13–18 months 19–24 months >24 months Average lactation duration: Never 1–3 months 4–6 months 7–9 months 10–12 months >12 months Normal weight and lactation Normal weight, no lactation Obese and lactation Obese, no lactation	0.92 (0.90, 0.96) Reference 0.90 (0.87, 0.93) 0.92 (0.87, 0.98) 0.93 (0.86, 0.99) 1.0 (0.91, 1.11) 1.06 (0.99, 1.14) Reference 0.90 (0.87, 0.94) 0.90 (0.85, 0.96) 0.93 (0.86, 0.99) 1.0 (0.95, 1.10) 1.02 (0.96, 1.08) Reference 1.06 (1.02, 1.11) 1.65 (1.58, 1.72) 1.85 (1.75, 1.90)	Age, smoking, PA, BMI>23.05, age at menarche, age at first pregnancy, number of children, OC

(*Continued*)

Table 3. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Oken et al. (2013) [37]	Belarus, Promotion of Breastfeeding Intervention Trial (PROBIT)	9,383 breastfeeding mothers who delivered a healthy singleton live birth at ≥37 weeks gestation; 31 units of medical care randomised to breastfeeding promotion intervention group or usual care; mean baseline age (SD): intervention group: 25.0 (5.0) and control group: 25.1 (4.9)	11.5 years postpar-tum	Measured or self-reported (previous diagnosis of HT or current use of anti-hypertensive medication) HT	Observational analyses regardless of treatment allocation: Lactation duration; <3 months ≥3-<6 months ≥6-<9 months ≥9-<12 months ≥12 months P-trend Exclusive lactation duration: <3 months ≥3-<6 months ≥6 months P-trend	No significant difference between the intervention and control groups for SBP (adjusted mean difference [95% CI] = 20.23 [22.71, 2.25]), DBP (adjusted mean difference [95% CI] = 20.74 [22.02, 0.53]), any HT (AOR [95% CI] = 0.88 [0.65, 1.19]) or diagnosed HT (AOR [95% CI] = 0.81 [0.45, 1.44]) Baseline and cluster-adjusted mean difference; Reference 0.10 (-0.67, 0.87) -1.19 (-2.12, -0.25) -0.71 (-1.85, 0.42) -0.57 (-1.48, 0.33) 0.05 Reference -0.39 (-1.16, 0.38) 0.40 (-1.16, 1.97) 0.75	Study site, polyclinic location, age, SES, smoking during pregnancy, number of children in the household

Abbreviations: BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, DASH = Dietary Approaches to Stop Hypertension, DBP = diastolic blood pressure, HRT = hormonal replacement therapy, HT = hypertension, MI = myocardial infarction, N/A, not applicable; OC = oral contraceptives, OR = odds ratio, PA = physical activity, RR = relative risk, SD = standard deviation, SES = socioeconomic status, SBP = systolic blood pressure, US = United States, WHR = waist-to-hip ratio.

[a] For the assessment of breastfeeding, self-reported measures included lactation history: defined as ever breastfeeding; lactation duration: length of time a woman breastfed a child; exclusive lactation duration: length of time a woman exclusively breastfed a child before introducing complementary foods; lifetime lactation duration: cumulative amount of time a woman breastfed across all pregnancies and average lactation duration: lifetime lactation duration divided by the total number of children. For lactation history, the reference category is the second category mentioned (e.g. for ever vs. never, never is the reference category).

[b] Odds ratio with 99% CI presented for this paper.

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Table 4. Summary of included studies with inflammatory markers, adipokines and subclinical cardiovascular disease as the outcomes.

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Cross-sectional/retrospective studies							
McClure et al. (2012) [29]	US, Women and Infant Study of Healthy Hearts (WISH)	569 premenopausal women who delivered a singleton live birth, following a pregnancy without complications; mean age (SD) = 35.6 (7) for women who breastfed any child <3 months; mean age (SD) = 39.6 (6) for women who breastfed ≥3 months	N/A 4–12 years after delivery	Measured subclinical CVD: carotid artery intima-media thickness, lumen diameter, adventitial diameter and carotid-femoral pulse wave velocity	Lactation duration for each child: Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months	Lumen diameter 0.13 (0.04, 0.22) 0.11 (0.002, 0.22) Reference Adventitial diameter 0.12 (0.02, 0.22) 0.10 (-0.02, 0.21) Reference Intima-media thickness 0.79 (0.41, 1.54) 0.51 (0.24, 1.09) Reference Carotid-femoral pulse wave velocity 0.21 (-0.10, 0.52) 0.02 (-0.34, 0.37) Reference	Age, ethnicity, SES, family history of diabetes/MI/ stroke, smoking, PA, vitamin supplementation, early adult BMI, current BMI, SBP, total chol, HDL-C, TG, CRP, glucose, insulin, optimism, anxiety, max. gestational weight gain, birth outcome, gestational age, infant birth weight, additional preterm births, years since last birth, parity
Schwarz et al. (2010) [30]	US, Study of Women's Health Across the Nation (SWAN)	297 women without prevalent CVD at baseline who delivered at least 1 singleton live birth; 45–58 years	N/A	Measured subclinical CVD: coronary and aortic calcification, carotid adventitial diameter, intima–media thickness and carotid plaque	Lactation duration for each child: Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months Never breastfed Breastfed any child <3 months Breastfed each child ≥3 months	Aortic calcification Reference 0.34 (0.09, 1.28) 0.19 (0.05, 0.68) Coronary calcification Reference 0.96 (0.28, 3.27) 0.43 (0.13, 1.49) Carotid plaque Reference 0.75 (0.18, 3.23) 0.45 (0.11, 1.84) Adventitial diameter Reference -0.12 (-0.35, 0.11) -0.04 (-0.26, 0.18) Intima-media thickness Reference 0.79 (0.27, 2.32) 0.93 (0.33, 2.67)	Study site, age, ethnicity, SES, family history of diabetes/MI/stroke, smoking, PA, dietary intake, vitamin supplementation, BMI, SBP, TG, total chol, HDL, CRP, glucose, insulin, perceived stress, depressed mood, menopausal status, parity
Prospective studies							

(*Continued*)

Table 4. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Stuebe et al. (2010) [33]	US, Project Viva	570 women with a singleton pregnancy; <22 weeks gestation at baseline; mean age (SD) at 3 years postpartum: no lactation: 36.0 (4.8); >0–<3 months lactation: 36.8 (6.0); 3–<6 months: 37.2 (5.3); 6–<12 months: 38.2 (4.6); ≥12 months: 38.8 (5.0)	3 years post-partum	Measured inflammato-ry markers: CRP and IL6 175 subjects had fasting blood samples	Lactation duration: Never >0-<3 months 3-<6 months 6-<12 months ≥12 months Exclusive lactation duration: Never >0-<1 months 1-<3 months 3-<6 months ≥6 months	No significant associations between either lactation duration or exclusive lactation duration and inflammatory markers. Adjustment for BMI before pregnancy eliminated unadjusted association with CRP.	Family history of type 2 diabetes, smoking, PA, dietary intake, intention to lose weight, self-reported weight at 12 months, pre-pregnancy BMI, gestational weight gain, gestational glucose tolerance, parity, OC
Stuebe et al. (2011) [34]	US, Project Viva	570 women with a singleton pregnancy; <22 weeks gestation at baseline; mean age (SD) at 3 years postpartum: no lactation: 36.0 (4.8); >0–<3 months lactation: 36.8 (6.0); 3–<6 months: 37.2 (5.3); 6–<12 months: 38.2 (4.6); ≥12 months: 38.8 (5.0)	3 years post-partum	Measured adipokines: leptin, adiponectin, ghrelin, peptide YY 175 subjects had fasting blood samples	Lactation duration: Never >0-<3 months 3-<6 months 6-<12 months ≥12 months Exclusive lactation duration: Never >0-<1 months 1-<3 months 3-<6 months ≥6 months	Lactation duration was associated with ghrelin (predicted mean = 749.5 for none vs. 852.9 pg/ml for ≥12 months lactation; p = 0.05) and peptide YY levels (predicted geometric mean = 55 for none vs. 63.4 pg/ml for ≥12 months lactation; p = 0.03). Lactation duration was not associated with leptin levels after adjustment for pre-pregnancy BMI. Exclusive lactation duration was associated with ghrelin (predicted mean = 790.6 for never exclusively breastfeeding vs. 1,008.1 pg/ml for 6 months exclusive breastfeeding; p<0.01). Non-linear association between lactation duration/exclusive lactation duration with adiponectin.	Age, race, family history of type 2 diabetes, smoking status, pre-pregnancy BMI, gestational weight gain, gestational glucose tolerance, parity; additional adjustment for lactation duration after introduction of complementary foods

Abbreviations: BMI = body mass index, chol = cholesterol, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, HDL-C = high-density lipoprotein cholesterol, IL-6 = interleukin 6, max = maximum, MI = myocardial infarction, N/A = not applicable; OC = oral contraceptives, OR = odds ratio, PA = physical activity, RR = relative risk, SBP = systolic blood pressure, SD = standard deviation, SES = socioeconomic status, TG = triglycerides, US = United States.

[a] For the assessment of breastfeeding, self-reported measures included lactation history: defined as ever breastfeeding; lactation duration: length of time a woman breastfed a child; exclusive lactation duration: length of time a woman exclusively breastfed a child before introducing complementary foods.

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Table 5. Summary of included studies with cardiovascular disease as the outcome.

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Cross-sectional/retrospective studies							
Schwarz et al. (2009) [36]	US, Women's Health Initiative (WHI)	139,681 parous, postmenopau-sal women with ≥1 live birth; 50–79 years	N/A	Self-reported; prevalence of CVD (MI, angina, CHF, peripheral arterial disease, revascularisation, stroke)	Lifetime lactation duration: Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend Never ≥13 months	 Reference 1.03 (0.98, 1.09) 0.95 (0.88, 1.02) 0.93 (0.85, 1.01) 0.89 (0.80, 0.98) 0.005 Reference 0.91 (0.85, 0.98), P = 0.008	Age, ethnicity, SES, family history of diabetes/MI/ stroke, smoking, PA, dietary intake, use of aspirin/ multivitamin, BMI, parity, HRT
Prospective studies							
Stuebe et al. (2009) [13]	US, Nurses' Health Study	89,326 parous women without a history of MI, angina or coronary artery bypass graft; 40–65 years	1986–2002	Self-reported incidence of MI (confirmed by physician review of medical records)	Lifetime lactation duration: None >0–3 months >3–6 months >6–11 months >11–23 months >23 months P-trend	 Reference (0.91, 1.11)[b] (0.88, 1.14)[b] (0.88, 1.18)[b] 0.93 (0.8, 1.07)[b] 0.77 (0.62, 0.94)[b] 0.02	Age, parental history of MI before age 60 years, smoking, alcohol, PA, dietary intake, use of aspirin/multivitamins, BMI at age 18 years, birth weight of subject, history of stillbirth, menopausal status, parity, HRT
Stuebe et al. (2009) [13] Birth in the last 30 years	-	-	-	-	Lifetime lactation duration; None >0–3 months >3–6 months >6–11 months >11–23 months >23 months P-trend	 Reference 0.94 (0.79, 1.12)[b] 0.98 (0.80, 1.21)[b] 0.96 (0.76, 1.21)[b] 0.89 (0.71, 1.10)[b] 0.66 (0.49, 0.89)[b] 0.02	-
Stuebe et al. (2009) [13] No birth in the last 30 years	-	-	-	-	Lifetime lactation duration; None >0–3 months >3–6 months >6–11 months >11–23 months >23 months P-trend	 Reference 1.04 (0.92, 1.18) 1.02 (0.86, 1.21) 1.02 (0.84, 1.24) 0.95 (0.78, 1.15) 0.90 (0.67, 1.19) 0.33	-

(*Continued*)

Table 5. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Schwarz et al. (2009) [36]	US, Women's Health Initiative (WHI)	139,681 parous, postmenopau-sal women with ≥1 live birth; 50–79 years	7.9	Self-reported incidence of CVD (CHD, stroke, CHF, angina, peripheral vascular disease, carotid artery disease, and coronary revascularization) validated by physician adjudication of medical records	Lifetime lactation duration: Never 1–6 months 7–12 months 13–23 months ≥24 months P-trend	 Reference (0.98, 1.08)[b] 0.97 (0.90, 1.04)[b] 0.98 (0.91, 1.05)[b] 0.93 (0.85, 1.02)[b] 0.12	Age, ethnicity, SES, family history of diabetes/MI/stroke, smoking, dietary intake, use of aspirin/ multivitamin, PA, BMI, parity, HRT
Gallagher et al. (2011) [35]	China	259,494 non-smoking female workers employed in the textile industry; 30->60 years	1989–2000	Measured; mortality from IHD, ischaemic stroke and haemorrhagic stroke, based on a death registry	Lactation duration; IHD: Never (parous) <6 months 7–12 months 13–24 months 25–36 months 37–48 months ≥49 months Ischaemic stroke: Never (parous) <6 months 7–12 months 13–24 months 25–36 months 37–48 months ≥49 months Haemorrhagic stroke: Never (parous) <6 months 7–12 months 13–24 months 25–36 months 37–48 months ≥49 months	 Reference 0.70 (0.42, 1.16)[b] 0.50 (0.33, 0.76)[b] 0.67 (0.46, 0.97)[b] 0.53 (0.36, 0.79)[b] 0.71 (0.48, 1.06)[b] 0.78 (0.53, 1.14)[b] Reference 1.02 (0.63, 1.66)[b] 1.05 (0.72, 1.54)[b] 0.90 (0.62, 1.31)[b] 1.15 (0.79, 1.67)[b] 1.21 (0.83, 1.77)[b] 1.20 (0.84, 1.72)[b] Reference 0.84 (0.63, 1.12)[b] 0.98 (0.79, 1.22)[b] 1.01 (0.82, 1.24)[b] 0.88 (0.71, 1.09)[b] 1.02 (0.82, 1.28)[b] 1.05 (0.84, 1.30)[b]	Age, number of live births

(*Continued*)

Table 5. (*Continued*)

First author (year)	Country and cohort designation	Participants	Mean follow-up or period (years)	Outcome assessment	Breastfeeding comparison categories[a]	Adjusted OR or RR (95% CI) by lactation history/ duration	Covariates
Natland Fagerhaug et al. (2013) [14] <65 years	Norway, Nord-Trøndelag Health Survey (HUNT2)	21,889 non-pregnant, parous women without prevalent MI, stroke, angina pectoris or diabetes prior to the first birth; 30–85 years	15	Measured; mortality from CVD, based on a death registry	Ever lactated Never lactated Nulliparous Lifetime lactation duration: None 7–12 months ≥24 months P-linear trend	Reference 2.86 (1.51, 5.39)[b] 0.41 (0.16, 1.04)[b] 2.77 (1.28, 5.99)[b] 0.55 (0.27, 1.09)[b] Reference 0.8	Marital status, SES, smoking, PA, BMI, TG, total chol, SBP, DBP, use of antihypertensive medication, diabetes, parity
Natland Fagerhaug et al. (2013) [14] ≥65 years	-	-	-	-	Ever lactated Never lactated Nulliparous Lifetime lactation duration:	Reference 1.11 (0.77, 1.69)[b] 1.20 (1.0. 1.44)[b] No clear associations (hazard ratios not reported in the study).	-

Abbreviations: BMI = body mass index, CHD = coronary heart disease, CHF = congestive heart failure, chol = cholesterol, CI = confidence interval, CVD = cardiovascular disease, DBP = diastolic blood pressure, HRT = hormone replacement therapy, IHD = ischaemic heart disease, MI = myocardial infarction, N/A = not applicable, OR = odds ratio, RR = relative risk, SBP = systolic blood pressure, SES = socioeconomic status, TG = triglycerides, US = United States.

[a] For the assessment of breastfeeding, self-reported measures included lactation history: defined as ever breastfeeding; lactation duration: length of time a woman breastfed a child; lifetime lactation duration: cumulative amount of time a woman breastfed across all pregnancies.

[b] Hazard ratios with 95% CI presented for this paper.

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with factors such as age, gestational weight gain and pre-pregnancy weight possibly confounding these relationships.

Type 2 diabetes. In a 2014 review and meta-analysis based on six cohort studies, the longest duration of lifetime lactation was associated with a 32% reduction in relative risk of type 2 diabetes compared with the shortest duration [16]. This finding was in line with a later review of the same primary studies [15] and an earlier systematic review [18].

MS. MS is a cluster of conditions which can increase the risk for diabetes and CVD. Table 1 describes studies with MS as the outcome. Five studies examined the association between breastfeeding and MS [12,22–24,31]. Studies adhered to the National Cholesterol Education Program Adult Treatment Panel III criteria [38] to define MS, which is based on the presence of three of more of the following risk determinants: abdominal obesity, elevated triglyceride levels, reduced high-density lipoprotein cholesterol levels, elevated blood pressure, and elevated fasting glucose levels [38]. The findings from the three cross-sectional studies, conducted among women of different age categories, were mixed [22–24]. One study from the US found a significant protective association of both lactation history and lifetime lactation

duration with MS in a dose-response manner in middle-aged, parous premenopausal women from various ethnic backgrounds [22]. Another US study reported a significant association between lactation history and the prevalence of MS in parous women aged ≥20 years. However, this association was no longer significant after additional adjustment for BMI [23]. The third study did not find any association between lactation history and the prevalence of the MS in postmenopausal Korean women [24].

Both prospective studies found significant protective effects of lifetime lactation duration on incident MS [12,31]. One study following Iranian women over 9 years observed a significant association between 13–23 months lifetime lactation duration and higher incidence of MS compared with ≥24 months [31]. The other study showed that lifetime lactation duration of 6–9 and >9 months was significantly associated with a lower incidence of MS compared with 0–1 month lactation, among American women of reproductive age followed over a 20-year period [12].

Metabolic risk factors. Table 2 provides a summary of studies with metabolic risk factors as the outcomes. Five studies (three cross-sectional/retrospective, two prospective) assessed the relation between breastfeeding and metabolic risk factors [25,26,32,33,36]. All three cross-sectional/retrospective studies reported a protective association of breastfeeding with metabolic risk factors [25,26,36]. One study involving Portuguese mothers who were examined at 4 years postpartum, showed that women who breastfed their child for >26 weeks were less likely to be obese and have and an adverse metabolic profile. However, there was no association between breastfeeding and excessive weight associated with a healthy metabolic profile [25]. Another cross-sectional/retrospective study found that lifetime lactation duration is associated in a dose-response fashion with a more favorable cardiovascular risk profile, including lipids, in a large sample of Norwegian mothers later in life [26]. Similarly, the third cross-sectional/retrospective study found a dose-response relationship between lifetime lactation duration and hyperlipidemia in a large sample of US mothers [36].

The findings from relatively small prospective studies were mixed [32,33]. One US prospective study examining 3-year changes in metabolic risk factors from pre-pregnancy to post-weaning showed that breastfeeding is associated with a more favorable metabolic risk profile in the postpartum period [32]. In contrast, the other US prospective study did not find any association between lactation duration and metabolic risk at 3 years postpartum after adjusting for pre-pregnancy BMI [33].

Hypertension. Table 3 describes studies with hypertension as the outcome. Seven studies examined the association between breastfeeding and hypertension [7,8,26–28,36,37]. Breastfeeding was associated with lower odds of hypertension in all four cross-sectional/retrospective studies [26–28,36]. Both lactation history and duration were associated with reduced odds of hypertension in middle-aged and older Chinese mothers [27]. Similarly, in a large sample of Australian women aged ≥45 years, lactation history was protective compared to parous women who never breastfed or nulliparous women [28]. Lifetime lactation duration of >6 months, or >3 months/child, was significantly associated with lower odds of hypertension, in women aged 45–64 years compared with parous women who did not breastfeed. The odds of hypertension decreased with longer breastfeeding durations and were mostly not significant in women ≥64 years. In another cross-sectional/retrospective study from Norway, while there were no clear associations in mothers ≥50 years, mothers aged <50 years who had never lactated had higher odds of hypertension than those who had lactated ≥24 months in their lifetime [26]. In contrast, lifetime lactation duration was significantly associated with lower odds of hypertension in postmenopausal US women ≥50 years [36].

Breastfeeding also appeared to be protective in two large prospective studies [7,8]. In a US cohort of parous women, those who did not breastfeed were more likely to develop

hypertension compared with those who breastfed their first child for ≥12 months or exclusively breastfed their first child for ≥6 months [7]. Lactation history, lifetime lactation duration between 1–18 months and average lactation duration between 1–9 months were also protective among a large cohort of premenopausal Korean women followed for six years [8]. In a large cluster RCT from Belarus, despite greater breastfeeding duration and exclusivity achieved among breastfeeding mothers randomized to a breastfeeding promotion intervention compared to usual care, there was no significant difference in blood pressure between mothers receiving the intervention and those allocated to the usual care group. However, this was not an RCT of breastfeeding per se but of factors aimed at promoting breastfeeding behaviour. In addition, a marginally significant association was found between lactation duration and lower blood pressure at 11.5 years postpartum in observational analyses in the same sample regardless of treatment allocation [37].

Inflammatory markers and adipokines. Table 4 provides a summary of studies with inflammatory markers, adipokines and subclinical cardiovascular disease as the outcomes. Only two papers from the same sample were identified [33,34]. In one paper, two inflammatory markers: C-reactive protein (CRP), commonly associated with cardiovascular health outcomes [39], and interleukin-6, a proinflammatory cytokine that induces the hepatic production of CRP [40], were examined, but neither was significantly related to lactation duration at 3 years postpartum among 175 women with fasting blood samples after adjusting for prepregnancy BMI [33]. The other paper [34] examined adipokines, which are cytokines secreted by adipose tissue that are involved in inflammatory responses and associated with metabolic disease risk [41]. At 3 years postpartum, longer lactation duration was associated with higher levels of ghrelin and peptide YY, both involved in appetite regulation and associated with reduced risk of metabolic disease [34].

Subclinical cardiovascular disease. Early physiologic changes in vascular health such as calcified atherosclerotic plaques and increases in carotid adventitial diameter can be detected and identify patients at increased risk of future cardiovascular events [42–44]. Two cross-sectional/retrospective studies from the US assessed the relationship between breastfeeding and subclinical cardiovascular disease [29,30]. Both studies have found non-breastfeeding mothers to be at increased risk of vascular changes associated with subsequent cardiovascular disease. Among premenopausal women assessed 4 to 12 years after delivery, mothers who never breastfed had larger carotid artery lumen and adventitial diameters, which are indicative of poorer cardiovascular health status, compared with mothers who breastfed all of their children for at least 3 months [29]. In another study involving an older sample of women between 45 to 58 years of age, the association between lactation and an increased adventitial diameter was not significant after adjustment for confounders. However, aortic calcification remained significantly associated with lactation duration [30]. McClure et al. [29] suggest that differences in the significance of findings between breastfeeding and adventitial diameter could be due to the younger age group and shorter time since pregnancy in their study.

Cardiovascular disease. Table 5 describes studies with cardiovascular disease as the outcome. A few studies investigated the relationship between breastfeeding and cardiovascular disease, and found protective effects of breastfeeding [13,36]. One US study examined both the self-reported prevalence and incidence (confirmed by physician adjudication of medical records) of cardiovascular disease in a large sample of parous, postmenopausal women [36]. In that study, increasing lifetime lactation duration was significantly associated with a lower prevalence of cardiovascular disease, compared with never breastfeeding. In particular, women who breastfed ≥13 months in their lifetime and women aged 50–59 years who had breastfed ≥7 months, were less likely to have prevalent cardiovascular disease. Although women aged 60–69 years with 13–23 months of lifetime lactation had lower odds of prevalent cardiovascular

Table 6. Summary of expected direction of associations[a] between breastfeeding and cardiovascular risk factors/outcomes.

	References	Number of cross-sectional/ retrospective studies			Number of prospective studies/ cluster randomized controlled trial		
		+	0	-	+	0	-
Cardiovascular risk factors							
Metabolic Syndrome	[12,22–24,31]	1	2		2		
Metabolic risk factors	[25,26,32,33,36]	2			1	1	
Hypertension	[7,8,26–28,36,37]	4			2	1	
Inflammatory markers	[33]					1	
Adipokines	[34]				1	1	
Subclinical cardiovascular disease	[29,30]	2	1				
Cardiovascular outcomes							
Prevalence/incidence of cardiovascular disease	[13,36]	1			1	1	
Cardiovascular disease mortality	[14,35]				2	1	

[a] The expected direction of each association was hypothesized based on existing literature and coded as: + (significant association in the hypothesized direction),–(significant association not in the hypothesized direction), 0 (non-significant association).

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disease than similar-aged women who had never breastfed, there were no significant associations observed in women aged 70–79 years [36].

In that same study, lifetime lactation duration was not associated with incident cardiovascular disease in the overall sample followed for 7.9 years [36]. However, compared to similar-aged women who never breastfed, significant cardiovascular benefits were seen in women in the younger age group, but not in the older age groups. In another large US study involving middle-aged and elderly women, women with a lifetime lactation duration ≥12 months had a reduced risk of incident myocardial infarction (confirmed by physician review of medical records) compared with parous women who had never breastfed [13]. A stronger inverse association was observed for women with ≥23 months of lifetime lactation and for those with a birth in the last 30 years.

Two prospective studies assessed the association between breastfeeding and cardiovascular disease mortality ascertained from death registries [14,35]. Among a large sample of Chinese non-smoking textile workers followed between 1989 and 2000, lactation duration was not significantly associated with mortality from ischaemic or haemorrhagic stroke [35]. However, compared to parous women who never breastfed, women who breastfed appeared to have a lower risk of mortality from ischaemic heart disease. In another study from Norway, mothers aged <65 years that never breastfed had nearly three times the risk of death from cardiovascular disease over 15 years compared with mothers with a lifetime lactation duration ≥24 months [14]. There was evidence for a U-shaped association with women who breastfed 7–12 months having almost half the risk of women who breastfed ≥24 months in their lifetime. There were no significant associations in women 65 years and over.

Overall pattern of associations. The pattern of associations across different outcomes is summarized in Table 6. Overall, 19 studies (10 cross-sectional/retrospective, 9 prospective) reported significant protective effects of breastfeeding, nine studies (3 cross-sectional/retrospective, 5 prospective, 1 cluster RCT) reported non-significant findings and none reported

detrimental effects of breastfeeding. Ten out of thirteen associations reported in cross-sectional/retrospective studies suggested that breastfeeding was associated with significant cardiovascular benefits. Although the evidence was less convincing, nine out of fifteen associations reported in prospective studies also indicated beneficial effects of breastfeeding. Out of all cardiovascular risk factors and outcomes considered, the evidence for significant protective effects of breastfeeding was most convincing for hypertension, although the evidence was mainly based on cross-sectional/retrospective studies. Three-quarters of high quality studies [7, 12, 13, 14, 22, 26, 28, 29, 30, 32, 34, 36] and 80% of medium quality studies [8, 27, 31, 35] reported significant protective effects of breastfeeding.

Discussion

This review synthesized the current evidence on the associations between breastfeeding and cardiovascular risk factors and outcomes, including MS, metabolic risk factors, hypertension, inflammatory markers, adipokines, subclinical cardiovascular disease and cardiovascular disease. Nearly all included studies were published in the last decade highlighting the rising interest in the maternal health benefits of breastfeeding. Overall, most studies reported significant protective effects of breastfeeding, several reported non-significant findings while there were no studies that reported detrimental effects of breastfeeding. The cardiovascular benefits of breastfeeding were present in most studies even after adjustment for multiple covariates, including socio-demographic, lifestyle factors (e.g. smoking, physical activity, dietary intake), BMI and parity. In addition, findings from included studies indicate that breastfeeding has favorable short-term and long-term cardiovascular health outcomes. Altogether, the evidence from medium-high quality studies suggests that breastfeeding is associated with several cardiovascular health benefits that can extend to later life, and supports health promotion strategies and interventions to increase breastfeeding. Notwithstanding, findings from this review should be interpreted with caution as the evidence gathered for each individual outcome is limited by the small number of observational studies. In particular, additional prospective studies of larger samples are needed.

Breastfeeding intensity and duration

For optimal child and maternal health benefits, the World Health Organization recommends exclusive breastfeeding for the first 6 months of life followed by two years or more of breastfeeding supplemented by complementary foods [45]. With the exception of four studies [7,33,34,37], most studies did not distinguish between exclusive breastfeeding, a measure of breastfeeding intensity, and breastfeeding supplemented by other foods. Several studies compared exclusive breastfeeding for $\geq$6 months with shorter durations of exclusive breastfeeding or non-exclusive breastfeeding, and found inconsistent associations with a range of cardiovascular outcomes [7,33,34,37]. Overall, additional studies that explore the association between exclusive breastfeeding and a range of short- and long-term cardiovascular health outcomes are needed.

Breastfeeding appears to be a protective factor for several maternal cardiovascular risk factors and outcomes, with evidence suggesting that increased duration may be associated with further benefits. Based on evidence from both cross-sectional/retrospective and prospective studies, benefits were reported for $\geq$24 months of lifetime lactation for most outcomes including metabolic risk factors [26,36], hypertension [28], the prevalence [36] and incidence of cardiovascular disease [13], and mortality from cardiovascular disease [14].

Dose-response

A dose-response relationship has been suggested between breastfeeding and various cardiovascular outcomes including MS, several metabolic risk factors, hypertension and the prevalence

of cardiovascular disease. A cross-sectional/retrospective study among parous pre-menopausal women found a dose-response association between lifetime lactation duration and MS [22]. However, this relationship was modified by parity and protective effects of breastfeeding were no longer observed after four births. A prospective study also found dose-response effects of lifetime lactation duration up to >9 months on incident MS developed over a 20-year period [12]. In two large cross-sectional/retrospective studies involving parous women <50 years [26] and postmenopausal women [36], inverse dose-response associations were observed between lifetime lactation duration up to ≥24 months and several maternal cardiovascular risk factors including lipid levels [26,36], blood pressure [26,36], and the prevalence of cardiovascular disease [36].

Although findings from these studies suggest that there is a dose-response relationship between breastfeeding and metabolic risk factors, additional evidence is needed, particularly from longitudinal studies. The possibility of a U-shaped relationship between breastfeeding and cardiovascular mortality [14] should also be further investigated.

Short vs long-term outcomes

A previous systematic review has evaluated the relationship between breastfeeding and postpartum weight change and has found inconclusive evidence [17]. In our systematic review, lactation was associated with maternal improvements in metabolic risk factors from preconception to post-weaning in one prospective study [32] while no association was detected in another prospective study at 3 years postpartum [33]. However, an association between breastfeeding and adipokine levels at 3 years postpartum was reported in the latter cohort [34].

Meanwhile, evidence from cross-sectional/retrospective studies among middle-aged and older women suggests that breastfeeding may have protective effects in later life against hypertension [22,28], metabolic risk [26,36] and cardiovascular disease [36].

Findings from prospective studies suggest that breastfeeding may be protective against the incidence of: MS among young and middle-aged women followed for 9 [31] or 20 years [12], hypertension among young and middle-aged women after 6 years of follow-up [7,8], cardiovascular disease among middle-aged [13] and older women [36] followed between 8–12 years, mortality from ischaemic heart disease over a 10 year period [35] and mortality from cardiovascular disease in women of various ages followed for 15 years [14].

Age, time since last birth and menopause. Findings from one cross-sectional/retrospective study [26] and a few prospective studies [14,28,36] suggest that the benefits from breastfeeding may diminish with age. In a large cross-sectional Norwegian study, significant associations between lifetime lactation duration and cardiovascular risk factors were observed in parous women <50 years. However, there were no clear associations in women >50 years [26]. Among three prospective studies, there were unclear associations with hypertension [28], the incidence of cardiovascular disease [36], or cardiovascular disease mortality [14] in women >60 [36] or >65 years of age [14,28]. Time since last birth may also have an effect on the association between breastfeeding and cardiovascular outcomes [13,26,36]. Among Norwegian mothers <50 years, the association between lifetime lactation duration and hypertension was attenuated after adjustment for time since last birth, while the association with metabolic risk factors remained similar [26]. In a large prospective cohort study, there was a stronger association between breastfeeding and incident myocardial infarction for women who gave birth in last the 30 years compared to women who had not [13]. Menopausal status may also influence the risk of cardiovascular disease. Among a large cohort of postmenopausal women, increasing lifetime lactation duration was associated with a lower prevalence of hypertension, diabetes, hyperlipidemia and cardiovascular disease [36]. There was also a significant association

between breastfeeding and the incidence of cardiovascular disease among women between 50–59 years of age, but not among women >60 years [36]. Whether older age, increasing time since last birth and menopause attenuate the association between breastfeeding and cardiovascular risk factors and outcomes requires further investigation.

Potential mechanisms

Breastfeeding increases metabolic expenditure approximately by 480 calories/day [46]. Although the effects of breastfeeding on postpartum weight change remains inconclusive [15,17], breastfeeding may lower cardiovascular risk by mobilizing fat stores accumulated during pregnancy. Breastfeeding may also have favorable effects on glucose metabolism, glycemic control and lipid metabolism [2–6]. The "reset hypothesis" in which breastfeeding "resets" maternal metabolism after pregnancy by reversing visceral fat accumulation and increases in insulin resistance, lipid and triglyceride levels has been proposed [47]. Hormones associated with breastfeeding such as prolactin and oxytocin may also exert effects on maternal blood pressure [48–50]. In addition, oxytocin may promote mother-child attachment and lead to reduced stress levels.

Methodological considerations

Several methodological issues should be considered in interpreting these findings. Observational studies are subject to residual confounding. Unmeasured confounders could include health-enhancing behaviors of breastfeeding mothers that distinguish them from non-breastfeeding mothers, and factors that influence breastfeeding initiation and duration such as pre-pregnancy BMI and pre-existing metabolic risk factors [51–53]. Breastfeeding measures were self-reported and recall bias may have led to misclassification of a woman's lactation history such as under- or over reporting of breastfeeding duration [54]. However, maternal recall of breastfeeding has been shown to be valid and reliable [55]. Differences in findings could be due to a number of factors that vary between studies including sample characteristics (e.g. country, setting), breastfeeding comparison categories, covariate adjustment and follow-up periods for prospective studies. Most included studies did not assess the exclusivity of breastfeeding, a measure of breastfeeding intensity. Temporal relationships could not be established from cross-sectional studies.

Strengths and limitations

The strengths of this review include systematic literature search, data extraction and summarization, an evaluation of the quality of included studies using established checklists, a range of maternal cardiovascular risk factors and outcomes examined, the inclusion of various breastfeeding comparison categories, the assessment of evidence relating to exclusive breastfeeding and dose-response relationship between breastfeeding and maternal outcomes, as well as a systematic and detailed approach in reporting findings. The limitations of this systematic review reflects limitations of the existing literature, such as a small number of prospective studies for each outcome of interest and methodological issues described above. Although the search terms used were comprehensive, there is a possibility that relevant studies were not identified by this systematic review.

Conclusion

Overall, the evidence from this systematic review suggests that breastfeeding is associated with maternal cardiovascular health benefits that extend from child-bearing years to later life.

However, additional longitudinal research is needed to investigate the association between breastfeeding and specific cardiovascular risk factors and outcomes and to further inform the evidence base.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Table. Search strategy used for MEDLINE, which was then adapted for EMBASE and CINAHL.
(DOCX)

S2 Table. Quality assessment criteria adapted from a 15-item checklist used by Van Uffelen et al. [20].
(DOCX)

S3 Table. Critical appraisal of included cross-sectional and prospective studies based on 15 quality assessment criteria.
(DOCX)

S4 Table. Critical appraisal of single cluster randomized controlled trial [37] based on quality assessment checklist developed by the Cochrane collaboration for assessing risk of bias in randomized studies [21].
(DOCX)

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S1 Table. Search strategy used for MEDLINE, which was then adapted for EMBASE and CINAHL.

1. Breast Feeding (as a subject heading)
2. Lactation (as a subject heading)
3. Milk, Human (as a subject heading)
4. Breast fed (as a text word)
5. Breastfe* (as a text word)
6. Lactat* (as a text word)
7. Breast milk (as a text word)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Maternal Health (subject heading)
10. Maternal health (as a text word)
11. Exp Women's Health (subject heading)
12. Reproductive history (subject heading)
13. (wom#n adj2 health) (as a text word)
14. (mother* adj2 health) (as a text word)
15. 9 or 10 or 11 or 12 or 13 or 14
16. Cardiovascular diseases (subject heading)
17. Hypertension (subject heading)
18. Risk factors (subject heading)
19. Coronary Artery Disease (subject heading)
20. Obesity (subject heading)
21. Diabetes Mellitus, Type 2 (subject heading)
22. Myocardial ischemia (subject heading)
23. Ischemic heart disease (as a text word)
24. Ischaemic heart disease (as a text word)
25. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 8 and 15 and 25
27. Limit 26 to (English language and female and humans)

S2 Table. Quality assessment criteria adapted from a 15-item checklist used by Van Uffelen et al. [31]

Item	Criteria	Description
1	Objectives	Are the objectives or hypotheses of the research described in the paper stated?
2	Study design	Is the study design presented?
3	Target population	Do the authors describe the target population they wanted to research?
4	Sample	Was a random sample of the target population taken? AND was the response rate 60% or more?
5	Sample	Is participant selection described?
6	Sample	Is participant recruitment described, or referred to?
7	Sample	Are the inclusion and/or exclusion criteria stated?
8	Sample	Is the study sample described? (minimum description=sample size, gender, age and an indicator of socio-economic status)
9	Sample	Are the numbers of participants at each stage of the study reported (Authors should report at least numbers eligible, numbers recruited, numbers with data at baseline, and numbers lost to follow-up)
10	Variables	Are the measures of breastfeeding and health outcome of interest described?

11	Data sources and collection	Do authors describe the source of their data (e.g., registry, health survey) AND did authors describe how the data were collected? (e.g., by mail)
12	Measurement	Was reliability of the measure(s) of breastfeeding mentioned or referred to?
13	Measurement	Was the validity of the measure(s) of breastfeeding mentioned or referred to?
14	Statistical methods	Were appropriate statistical methods used and described, including those for addressing confounders?
15	Statistical methods	Were the numbers/percentages of participants with missing data for breastfeeding and the health outcome indicated AND If more than 20% of data in the primary analyses were missing, were methods used to address missing data?

S3 Table. Critical appraisal of included cross-sectional/retrospective and prospective studies based on 15 quality assessment criteria.

First author (publication year) / Quality assessment criteria addressed[a]	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	Overall count[b]	Overall study quality rating[c]
Cho (2009) [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	U	13 Y, 2 U	High
Ram (2008) [22]	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14 Y, 1 U	High
Cohen (2006) [23]	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	N	N	Y	U	10 Y, 3 U, 2 N	Medium
Gunderson (2010) [12]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	13 Y, 2 N	High
Gunderson (2007) [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	13 Y, 2 N	High
Ramezani Tehrani (2014) [31]	Y	Y	Y	U	Y	Y	U	U	U	Y	Y	Y	Y	Y	N	7 Y, 4 U, 1 N	Medium
Zhang (2015) [27]	Y	Y	Y	U	Y	N	N	Y	N	Y	Y	N	N	Y	U	8 Y, 2 U, 5 N	Medium
Lupton (2013) [28]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	12 Y, 3 N	High
Lee (2005) [8]	Y	Y	Y	N	Y	Y	Y	U	U	Y	Y	N	N	Y	U	9 Y, 3 U, 3 N	Medium
Stuebe (2011) [7]	Y	Y	Y	U	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	11 Y, 1 U, 3 N	High
McClure (2012) [29]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	12 Y, 3 N	High
Schwarz (2010) [30]	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	N	Y	Y	Y	12 Y, 2 U, 1 N	High
Gallagher (2011) [35]	Y	Y	Y	N	Y	Y	U	Y	U	Y	Y	N	N	Y	U	9 Y, 3 U, 3 N	Medium
Natland (2012) [26]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14 Y, 1 N	High
Stuebe (2009) [13]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	13 Y, 2 N	High
Henriques (2015) [25]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	12 Y, 2 N	High
Schwarz (2009) [36]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	13 Y, 2 N	High
Stuebe (2011) [34]	Y	Y	Y	N	Y	Y	Y	U	Y	Y	Y	N	N	Y	Y	11 Y, 1 U, 3 N	High
Natland (2013) [14]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14 Y, 1 N	High
Stuebe (2010) [33]	Y	Y	Y	N	Y	Y	Y	U	Y	Y	Y	N	N	Y	Y	11 Y, 1 U, 3 N	High

Abbreviations: N=No, U=Unclear, Y=Yes.

[a] Quality assessment criteria addressed were based on a checklist used by Van Uffelen et al. [20] and related to 15 criteria listed and described in S2 Table.

[b] Each individual criteria was allocated a Y (yes) if it was met/addressed, N (no) if it was not met or U (unclear) if it was unclear whether the criteria was met. An overall count of the total number of individual criteria that were met, not met and that were unclear is provided.

[c] An overall study quality rating was allocated based on the total number of criteria that were met (i.e., total number of "yes"). Studies were rated as: "low quality" if ≤1/3 of individual criteria were met, "medium quality" if >1/3-≤2/3 of individual criteria were met and "high quality" if >2/3 of criteria were met.

S4 Table. Critical appraisal of single cluster randomized controlled trial [37] based on quality assessment checklist developed by the Cochrane Collaboration for assessing risk of bias in randomized studies [21].

Quality assessment criteria	Was criteria met/addressed? [a]
Random sequence generation	Yes
Allocation concealment	Yes
Blinding of participants and personnel	No
Blinding of outcome assessment	No
Completeness of outcome data	Yes
Accurate outcome reporting	Yes
Other sources of bias addressed	Yes
Overall count[b]	5 Yes, 2 No
Overall study quality rating[c]	High

[a] Each individual criteria was allocated a "yes" if it was met/addressed, "no" if it was not met or "unclear" if it was unclear whether the criteria was met.

[b] An overall count of the total number of individual criteria that were met, not met and that were unclear is provided.

[c] An overall study quality rating was allocated based on the total number of criteria that were met (i.e., total number of "yes"). Studies were rated as: "low quality" if ≤1/3 of individual criteria were met, "medium quality" if >1/3-≤2/3 of individual criteria were met and "high quality" if >2/3 of criteria were met.

6.5 CONCLUDING SUMMARY FOR THIS CHAPTER AND KNOWLEDGE GAINED FROM THIS STUDY

To our knowledge, this was the first study to systematically summarise the evidence for an association between breastfeeding and metabolic syndrome, hypertension and CVD. Overall, 21 studies were included in the systematic review. Most studies reported significant short- and long-term protective effects of breastfeeding and supported health promotion strategies to increase breastfeeding in mothers to derive health benefits. However, one of the research gaps identified in this study was that the evidence for each individual outcome was provided by a limited number of prospective cohort studies.

CHAPTER SEVEN:

Breastfeeding and cardiovascular disease hospitalisation and mortality in parous women: Evidence from a large Australian cohort study

7.1 PREFACE TO THE CHAPTER

This chapter presents findings from a paper examining the association between breastfeeding and CVD-related hospitalisation and mortality among parous women from the 45 and Up Study cohort. The version of the paper that has been accepted for publication forms this chapter and is presented in manuscript format. Supplementary material accompanying the submitted manuscript is also included in this chapter. The paper addresses specific aim #4 of this thesis as described in Chapter 1. Dissemination of this research and author contributions for this paper are described below.

7.2 RESEARCH DISSEMINATION

The research presented in this chapter has been disseminated as follows:

Paper accepted for publication and currently in press

Nguyen B, Gale J, Nassar N, Bauman A, Joshy G, Ding D. Breastfeeding and CVD hospitalisation and mortality in parous women: Evidence from a large Australian cohort study. *Accepted for publication and currently in press. Submitted to the Journal of the American Heart Association.*

Impact factor 5.117

Published conference abstract

Nguyen B, Gale J, Nassar N, Bauman A, Joshy G, Ding D. Breastfeeding and cardiovascular disease hospitalisation and mortality in mothers from a large Australian cohort study. *Revue d'Epidemiologie et de Sante Publique* 2018; 66 (Suppl 5): S310. Available from; http://doi.org/10.1016/j.respe.2018.05.192

Conference presentations

Nguyen B, Bauman A, Ding D. Gale J, Nassar N, Bauman A, Joshy G, Ding D. Breastfeeding and CVD hospitalisation and mortality in mothers from a large Australian cohort study. *European Congress of Epidemiology*, Lyon, France, 2018. [Poster presentation]

Nguyen B, Bauman A, Ding D. Gale J, Nassar N, Bauman A, Joshy G, Ding D. Breastfeeding, CVD incidence and CVD mortality in a large Australian cohort. *Sax Institute 45 and Up Study Collaborators' Annual Meeting,* Sydney, Australia, 2017. [Oral presentation] – **Selected for 45 and Up Study media release leading to interview with the Australian Associated Press and radio interviews.**

Nguyen B. Breastfeeding to your heart's content. *3rd Annual Charles Perkins Centre Symposium*, Sydney, Australia, 2017. [Oral Presentation] – **Awarded best oral presentation.**

7.3 AUTHOR ATTRIBUTION STATEMENT

I, Binh Nguyen, was responsible for designing the study, analysing and interpreting data, writing drafts of the manuscript, submitting the manuscript, responding to reviewers' comments, and coordinating submission and publication of the manuscript.

My co-author, J. Gale, conducted the statistical analysis. My co-authors, J. Gale, N. Nassar, A. Bauman, G. Joshy and D. Ding, helped to design the study, interpret data, draft the manuscript, and revise the manuscript critically for important intellectual content.

All authors have read and approved the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.

Signature:

Dr. Ding (Melody) Ding

7.4 PAPER IN MANUSCRIPT FORMAT FOLLOWED BY CORRESPONDING SUPPLEMENTARY MATERIAL

Title

Breastfeeding and cardiovascular disease hospitalisation and mortality in parous women: Evidence from a large Australian cohort study

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Abstract

Background. Few studies have investigated the longitudinal association between breastfeeding and maternal cardiovascular disease (CVD) outcomes. This study examined the association between breastfeeding and CVD hospitalisation and mortality in a large Australian cohort.

Methods and Results. Baseline questionnaire data (2006-2009) from a sample of 100,864 parous women aged ≥45 years from New South Wales, Australia, were linked to hospitalisation and death data until June 2014 and December 2013, respectively. Analysis was restricted to women without self-reported medically diagnosed CVD at baseline or without prior CVD hospitalisation six years prior to study entry. Never versus ever breastfeeding and average breastfeeding duration per child, derived from self-reported lifetime breastfeeding duration and number of children, and categorised as never breastfed, <6, >6-12, >12 months/child, were assessed. Cox proportional hazards models were used to explore the association between breastfeeding and CVD outcomes. Covariates included socio-demographic characteristics, lifestyle risk factors, and medical and reproductive history.

There were 3,428 (3.4%) first CVD-related hospital admissions and 418 (0.4%) deaths during a mean follow-up time of 6.1 years for CVD hospitalisation, and 5.7 years for CVD mortality. Ever breastfeeding was associated with lower risk of CVD hospitalisation (adjusted HR [95% CI]=0.86 [0.78, 0.96]; p=0.005) and CVD mortality (adjusted HR [95% CI]: 0.66 [0.49, 0.89]; p=0.006) compared to never breastfeeding. Breastfeeding ≤12 months/child was significantly associated with lower risk of CVD hospitalisation.

Conclusions. Breastfeeding is associated with lower maternal risk of CVD hospitalisation and mortality in middle-aged and older Australian women. Breastfeeding may offer long-term maternal cardiovascular health benefits.

Keywords

Breastfeeding, lactation, maternal health, cardiovascular diseases, prospective studies

Clinical Perspective

1) **What is new?**
    - Findings from this study add to the growing evidence base for the long-term benefits of breastfeeding for maternal cardiovascular health
    - Among parous women ≥45 years and over, ever breastfeeding and average breastfeeding duration per child up to 12 months were associated with substantially lower risk of developing and dying from cardiovascular disease
    - Findings were mostly consistent among women from different socio-economic backgrounds and with different lifestyle risk

2) **What are the clinical implications?**
    - This study provides evidence that breastfeeding is associated with long-term benefits for maternal cardiovascular health, in addition to its known benefits for infants and mothers
    - Breastfeeding may be promoted as an additional strategy by which parous women can reduce their risk of developing and dying from CVD

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death for women worldwide [1]. Preventing CVD through modifying known lifestyle risk factors, such as being overweight and an unhealthy diet, is a key public health priority. While changes in established lifestyle risk factors can lead to substantial reduction in the risk of developing CVD, prevention approaches should also incorporate emerging knowledge about novel risk factors of CVD, including behaviours that are specific to women. There has been an urgent, global call to conduct more gender-specific research to better inform public health strategies [2]. Gender differences exist in the epidemiology, diagnosis, risk profile, and treatment of CVD. Compared to men, women generally develop CVD at a later age, present with different symptoms and risk factors, are underdiagnosed, and respond differently to various treatments [2].

Breastfeeding has emerged in recent years as a lifestyle risk factor that may be associated with CVD, however the evidence is limited by the small number of observational studies, particularly longitudinal studies [3]. The prevalence of early initiation of breastfeeding within one hour of birth is approximately 30% in high-income countries [4] and around 79% of newborns in high-income countries are ever breastfed [5]. Globally, the prevalence of exclusive breastfeeding for infants under 6 months of age is approximately 43% [5]. During pregnancy, profound metabolic changes occur in a mother's body to support fetal growth and prepare for lactation [6]. It has been hypothesised that breastfeeding, which increases metabolic expenditure by an estimated 480 kcal/day, may enable a more rapid reversal of metabolic changes in pregnancy, including improved insulin sensitivity, lipid metabolism and greater mobilisation of accumulated fat stores, thereby "resetting" maternal metabolism after pregnancy and potentially reducing maternal risk of cardiometabolic disease [7]. Multiple studies have reported the short-term benefits of

breastfeeding including lipid homeostasis [8,9], glucose homeostasis and insulin sensitivity [10,11]. However, whether these benefits can contribute to long-term maternal health are unclear.

Emerging evidence suggests that breastfeeding may reduce the risk of developing type 2 diabetes [12], hypertension [13], and the metabolic syndrome [14] later in life. Although a number of studies have examined the associations between breastfeeding and CVD outcomes such as the incidence of CVD [3,15-18] or death from CVD [3,19-22], findings from these studies are inconclusive.

An important issue to consider in interpreting these observational studies is confounding [3]. Mothers who have breastfed tend to be older, from a higher socio-economic background, have achieved higher levels of education and participate in health-promoting behaviours in comparison to non-breastfeeding mothers [23,24]. Maternal characteristics, such as living in lower socio-economic areas, have been highly associated with not breastfeeding over subsequent births [25], but residual confounding due to unmeasured factors may remain an issue. These socio-economic factors and health-promoting behaviours may also potentially bias the association between breastfeeding and CVD outcomes, and while previous studies have adjusted for their confounding effects [14-17,20,21], they did not investigate potential effect modification by socio-economic status and overall lifestyle.

The aims of this paper were to examine the association between breastfeeding and CVD hospitalisation and mortality in a large cohort of middle-aged and older parous women. Findings from this study can help build the evidence base for breastfeeding as an additional strategy to prevent CVD.

2. Methods

The authors declare that all supporting data are available within the article (and its online supplementary files).

2.1. Study population

The Sax's Institute's 45 and Up Study is a large-scale prospective cohort study of 123,815 men and 143,073 women aged 45 years and over residing in the state of New South Wales (NSW), Australia. From 2006 to 2009, potential participants were randomly sampled from the Department of Human Services enrolment database, the national health insurance provider, and were invited to take part in the study. Individuals joined the study by completing a postal questionnaire and providing informed consent for follow-up which included linkage of questionnaire data to population health databases. The study methods have been described in detail elsewhere [26].

We included all women who completed a baseline questionnaire. Women who reported that they had ever been diagnosed with or recently treated for CVD (self-reported heart disease, stroke or blood clot: n=21,797) or with a hospital admission in the six years prior to study entry (with a CVD diagnosis code in any diagnostic field or a CVD-related procedure code in any procedure code field [27]; n=13,323) were excluded from analysis. We further excluded those who were nulliparous (never given birth, n=15,654) or with unknown parity (n=918) at baseline and parous women with unknown breastfeeding duration (n=2,187). The final study sample included 100,864 women with reported breastfeeding duration. A participant flow chart for this study is provided in **Figure 1**.

The 45 and Up Study received ethics approval from the University of NSW Human Research Ethics Committee. Approval to use data from the 45 and Up Study for this paper was obtained from the NSW Population and Health Services Ethics Committee.

2.2. Measurement

2.2.1. Exposure. The baseline questionnaire for women (available at http://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/) included self-reported information on socio-demographic and lifestyle factors, height and body weight, medical and reproductive history. Women were asked to report the number of children they had given birth to and also the cumulative amount of time spent breastfeeding across all pregnancies, based on the question: "For how many months, in total, have you breastfed?" The average breastfeeding duration per child was derived from answers to these questions and categorised as never breastfed, >0 to 6 (<6) months, >6 to 12 months, >12 months. Breastfeeding was also explored as a binary variable in terms of whether a woman had ever versus never breastfed (also referred to as breastfeeding history).

2.2.2. Outcomes. The baseline questionnaire data were linked to hospital data from the NSW Admitted Patient Data Collection (APDC; until June 2014), mortality data from the NSW Registry of Births, Deaths, and Marriages (until June 2014), and data on causes of death from the Cause of Death Unit Record File (until December 2013) by the Centre for Health Record Linkage (CHeReL, NSW, Australia) using probabilistic record linkage methods and a commercially available software (Choice-Maker, ChoiceMaker Technologies Inc.). The probabilistic data linkage conducted by CHeReL has been reported to be highly accurate with false-positive and false-negative rates below 0.4% (http://www.cherel.org.au/quality-assurance).

A recent study has also shown that the accuracy of probabilistic linkage is unlikely to vary by socio-economic status in older adults [28].

The APDC is a complete census of all public and private hospital admissions in NSW that includes details of admissions such as dates of admission and discharge, and records all related diagnoses for each admission. These are coded using the World Health Organization International Classification of Diseases, 10th revision– Australian Modification (ICD10-AM) system. The NSW Registrar of Births, Deaths, and Marriages captures all deaths in NSW with causes subsequently coded using the ICD10-AM classification. In both data sources, the first CVD hospitalisation or death since baseline was based on a primary diagnosis of CVD of either ischemic heart disease (IHD; ICD10-AM codes: I20-I25) or cerebrovascular disease (ICD10-AM codes: I61-I67, I69) [29,30].

2.2.3. Covariates. Multivariable analyses were adjusted for a range of socio-demographic and lifestyle factors, and medical and reproductive history based on self-reported responses in the baseline survey. Socio-demographic variables included age (45-54, 55-64, ≥65 years), country of birth (Australia/other), highest educational qualification (≤10 years of schooling, high school/trade apprenticeship/certificate/diploma, university degree/higher), marital status (married/living with a partner or single/widowed/divorced/separated) and area-level socio-economic status (population-level quintiles based on the Socio-Economic Indexes For Area - Index of Relative Socio-Economic Disadvantage [31]). Lifestyle factors were based on responses at baseline and used as a marker of health-related behaviours. These included body mass index (kg/m^2; calculated as weight divided by height squared), smoking status (never, past, current), alcohol intake (≤14 or >14 drinks/week [32]), physical activity (assessed using validated questions from the Active Australia Survey [33]; categorised as <150, 150-299, ≥300 minutes

per week), multi-vitamin use (for most of the last four weeks; yes/no), omega 3 or fish oil use (yes/no), use of aspirin (yes/no), and oral contraceptive use (ever/never). Reproductive history was based on number of children given birth to (1, 2, 3, ≥4), mother's age for first child, mother's age for last child. Medical history was assessed using family history of CVD (yes/no), family history of hypertension (yes/no), family history of diabetes (yes/no), self-reported hypertension/recent treatment for hypertension (yes/no), and self-reported diabetes/recent treatment for diabetes (yes/no).

2.3. Statistical analysis

Baseline participant characteristics by breastfeeding history and duration are presented as means (standard deviation [SD]) for continuous variables and as percentages for categorical variables. Differences in baseline characteristics were assessed using chi-square tests for categorical variables, student t-tests for continuous variables with binary breastfeeding categories, and F statistics from ANOVA for continuous variables with multiple lactation categories. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were estimated for associations between either breastfeeding history or average breastfeeding duration per child and CVD outcomes by using Cox proportional hazards models. Separate models were used for CVD hospitalisations and CVD deaths with a time scale in years. In the analyses of incident CVD hospitalisation, CVD death before hospitalisation was not treated as a competing outcome, instead participants were censored at death irrespective of cause of death. Eligible women contributed person-years from the date of recruitment until admission date, date of death or end of follow-up (18 June 2014), which ever was the earliest; end of follow up was 31 December 2013 for analyses of CVD mortality. Proportionality assumptions were verified based on the methods of Lin et al. [34]. The "never breastfed" category was used as the reference category.

Left-truncated data were used to adjust for different CVD risk exposure times for each woman before baseline entry into the study [35]. This approach helped to account for differences in the time that some women may have been diagnosed with CVD in the months or years prior to enrolment in the study. For each of the CVD outcomes, four sequential models were used: unadjusted models (model 1), models adjusted for parity and socio-demographic characteristics (number of children, age, country of birth, educational level, marital status, area-level socio-economic status; model 2), models further adjusted for lifestyle factors (body mass index, smoking status, alcohol intake, physical activity; model 3), and models further adjusted for medical and reproductive covariates (multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes; model 4). To account for potential interaction by socioeconomic status and lifestyle risk, analyses were stratified by educational attainment and a healthy lifestyle index, used as a marker for CVD lifestyle risk factors. The healthy lifestyle index has been adapted from a lifestyle risk index previously developed using the 45 and Up Study cohort [36] and the Healthy Heart Score developed by Harvard School of Public Health [37]. It is based on the following six lifestyle risk factors scored individually as healthy (score=1) or not healthy (score=0): body mass index (<25 kg/m^2=1, ≥25 kg/m^2=0), physical activity level (<150 min/week=1; ≥150 min/week=0), smoking status (past/current smoker=0; never smoker=1), alcohol intake (≤14 drinks/week=1; >14 drinks/week=0), sleep (>7-<9 hours/day=1; <7 hours/day or >9 hours/day=0), fruit and vegetable intake (<2 serves of fruit/day and <3 serves of fruit/day=0; ≥2 serves of fruit/day and ≥3 serves of vegetables/day=1). For the stratified analyses, the healthy

lifestyle index was dichotomised as either healthy (sum of scores=5-6) or not healthy (sum of scores=0-4). Interactions were considered significant if $p<0.05$. Statistical significance was defined as $p<0.05$ and analyses were conducted using SAS version 9.3 (SAS Institute Inc.).

3. Results

3.1. Participant characteristics

Table 1 shows baseline socio-demographic characteristics and parity of the 100,864 parous women included in our study. The mean age of the sample was 60.2 (SD: 10.2) years. More than three-quarters (76.7%) of women were born in Australia, more than a third (40%) had ≤10 years of education, three quarters (75.4%) were married, and nearly two thirds (61.3%) belonged to the three lowest socioeconomic population-level quintiles. Of all parous women, 87.6% had a history of breastfeeding. On average, women had 2.7 (SD: 1.2) children and breastfed for 5.4 (standard deviation [SD]: 5.4) months per child. Compared to women who never breastfed, women who ever breastfed were more likely to be younger at baseline, have more children, a higher level of education, be married/living with a partner and live in an area with higher socioeconomic quintile. Women that had ever breastfed were also less likely to be obese, smoke and were more likely to engage in higher levels of physical activity and consume omega 3 or fish oil. The 45-54 years age group was more likely to have a higher breastfeeding duration per child than the older age groups. Those who breastfed >12 months on average per child were more likely to have a university degree. The lifestyle, medical and reproductive characteristics of women at baseline are presented in **Supplementary Table 1**.

3.2. Breastfeeding and CVD hospitalisation/mortality

Supplementary Table 2 presents HR and 95% CI for the incidence of CVD hospitalisation and mortality by breastfeeding history. During a mean follow-up of 6.1 years for CVD hospitalisation, and 5.7 years for CVD mortality, there were 3,428 (3.4%) first CVD-related admissions and 418 (0.4%) deaths. Compared to parous women who never breastfed, women who ever breastfed had lower risk of CVD hospitalisation (model 4: HR: 0.86; 95% CI: 0.78, 0.96; p=0.005) and mortality from CVD (model 4: HR: 0.66; 95% CI: 0.49, 0.88; p=0.006), in both unadjusted and adjusted models (p<0.01).

Table 2 shows HR and 95% CI for the incidence of CVD hospitalisation and mortality by average breastfeeding duration per child. In both unadjusted and adjusted models, women who breastfed on average >0-6 months or >6-12 months per child had lower risk of CVD hospitalisation (model 4, <6 months: 0.86 (0.78, 0.96); >6-12 months: 0.85 [0.75-0.97]) and mortality (model 4, <6 months: 0.69 (0.51, 0.94); >6-12 months: 0.59 [0.41-0.84]), compared to women who never breastfed.

3.3. Stratified analyses

Overall, none of the tests for interaction were statistically significant (all p>0.05). In the stratified analysis by education, the association between breastfeeding and CVD outcomes were similar across education strata (**Supplementary Table 3**). While, in the stratified analysis by healthy lifestyle index (**Supplementary Table 4**), the association between breastfeeding and CVD hospitalisation was non-significant in those with lower lifestyle scores ("not healthy") while protective in those with higher lifestyle scores ("healthy"). However, the association with CVD mortality was similarly protective in those with low and high lifestyle scores.

4. Discussion

In this large cohort of parous women aged 45 years and over, ever breastfeeding and average breastfeeding duration up to 12 months per child were associated with lower risk of incident CVD hospitalisation and CVD mortality. Following adjustment for socio-demographic, lifestyle-related and reproductive variables, ever breastfeeding was associated with a 14% lower risk of CVD hospitalisation and a 34% lower risk of mortality from CVD compared to never breastfeeding. Average breastfeeding duration per child up to 12 months was significantly associated with a ~15% lower risk of incident CVD and a 30-40% lower risk of CVD mortality compared to never breastfeeding. Findings were mostly consistent among women from different socio-economic backgrounds and with different lifestyle risk.

This longitudinal study provides further evidence that among childbearing women breastfeeding may offer long-term cardiovascular health benefits. The protective nature of the association between breastfeeding history and CVD outcomes is generally consistent with findings from the few previous studies which have examined similar associations among parous women from large cohorts (**Supplementary Table 5**) [15,16,20]. Differences between studies in the magnitude of the associations could be due to variation in follow-up periods, types of CVD and outcomes examined, covariate adjustment, and cohort characteristics. Compared with previous studies, this study was novel in that it examined associations in an Australian setting, included more socio-demographic and lifestyle covariates, and stratified analyses by socio-economic status and a healthy lifestyle index.

While previous studies have typically expressed breastfeeding duration in terms of lifetime breastfeeding duration, we chose to present breastfeeding duration as the average duration per child to help standardise findings, better account for parity and facilitate interpretation of

findings. We modelled average breastfeeding duration as a categorical variable due to the non-linearity of the distribution and chose clinically relevant cut-points based on breastfeeding guidelines. This study showed that an average breastfeeding duration per child up to 12 months was associated with lower risk of incident CVD hospitalisation and mortality compared with never breastfeeding. To our knowledge, there have been only two previous studies that have examined the association between average breastfeeding duration per child and CVD outcomes (**Supplementary Table 5**) [15,16] and both have reported inverse associations. In the case-cohort study nested within EPIC, an average breastfeeding duration ≥6 months, the highest breastfeeding duration considered, was associated with a 33% lower risk of incident IHD [15]. In the China Kadoorie Biobank study, each additional 6 months of breastfeeding per child was associated with a 4% and 3% lower risk of incident IHD and stroke, respectively [16]. However, different breastfeeding measures and study settings may limit the comparability of findings across studies.

In the present study, there was no clear evidence for a dose-response relationship between average lactation duration per child and CVD outcomes. In agreement with findings from our study, there was no solid evidence for a threshold or dose-response effect in the few studies that have examined average breastfeeding duration per child [15,16]. While inconsistent associations have been shown between lifetime breastfeeding duration and CVD mortality, findings from some studies suggest a potential threshold effect [18] or a U-shaped association [21]. However, further longitudinal research is needed.

4.1. Strengths and limitations

Strengths of this study include a large cohort size and prospective follow-up which enabled us to examine the association between breastfeeding and long-term cardiovascular outcomes.

Compared with previous studies, this study adjusted for a comprehensive range of covariates including relevant socio-demographic, lifestyle and reproductive factors, and sensitivity analyses stratified by socio-economic status and a healthy lifestyle index were conducted.

Several limitations should be mentioned. As for all observational studies, residual confounding may be an issue. Mothers that have breastfed may generally lead healthier lifestyles and come from higher socio-economic backgrounds [23,24] that could have contributed to the observed associations. However, adjusting for socio-economic factors and lifestyle-related covariates did not alter the findings of this study, and associations appeared mostly consistent across different education and lifestyle categories. Some of the findings should nonetheless be interpreted with caution due to small cell sample sizes in some of the stratified analyses, and particularly in relation to CVD mortality. Our results may also be subject to reverse causation. From the data collected, we could not assess whether women had pre-existing metabolic conditions such as obesity and type 1 diabetes, or conditions during pregnancy such as pre-eclampsia and gestational diabetes, which could have unfavourably influenced breastfeeding practice [38-40]. Breastfeeding duration was assessed retrospectively many years later and may be prone to recall bias which can lead to under- or over- reporting of breastfeeding duration [41]. However, maternal recall of lactation has been shown to be a valid and reliable measure [41] even many years following weaning [42]. Finally, it was also not possible to assess the exclusivity of breastfeeding (i.e. whether other complementary foods were being offered to breastfed children), which is a measure of breastfeeding intensity.

4.2. Implications and conclusions

With CVD being the leading cause of death in women, it is important to explore a range of strategies by which CVD can be prevented, involving established as well as emerging lifestyle

behaviours. This study provides evidence that ever breastfeeding and average breastfeeding duration up to 12 months per child were associated with substantially lower risk of CVD hospitalisation and mortality. While further longitudinal studies are needed to achieve greater consensus, findings from this study add to the growing evidence base for the long-term benefits of breastfeeding for maternal cardiovascular health, promoting added benefits of breastfeeding beyond known benefits for infants and short-term benefits for mothers, and support breastfeeding as an important strategy by which parous women can reduce their risk of developing and dying from CVD.

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Conflict of Interest Disclosures

None.

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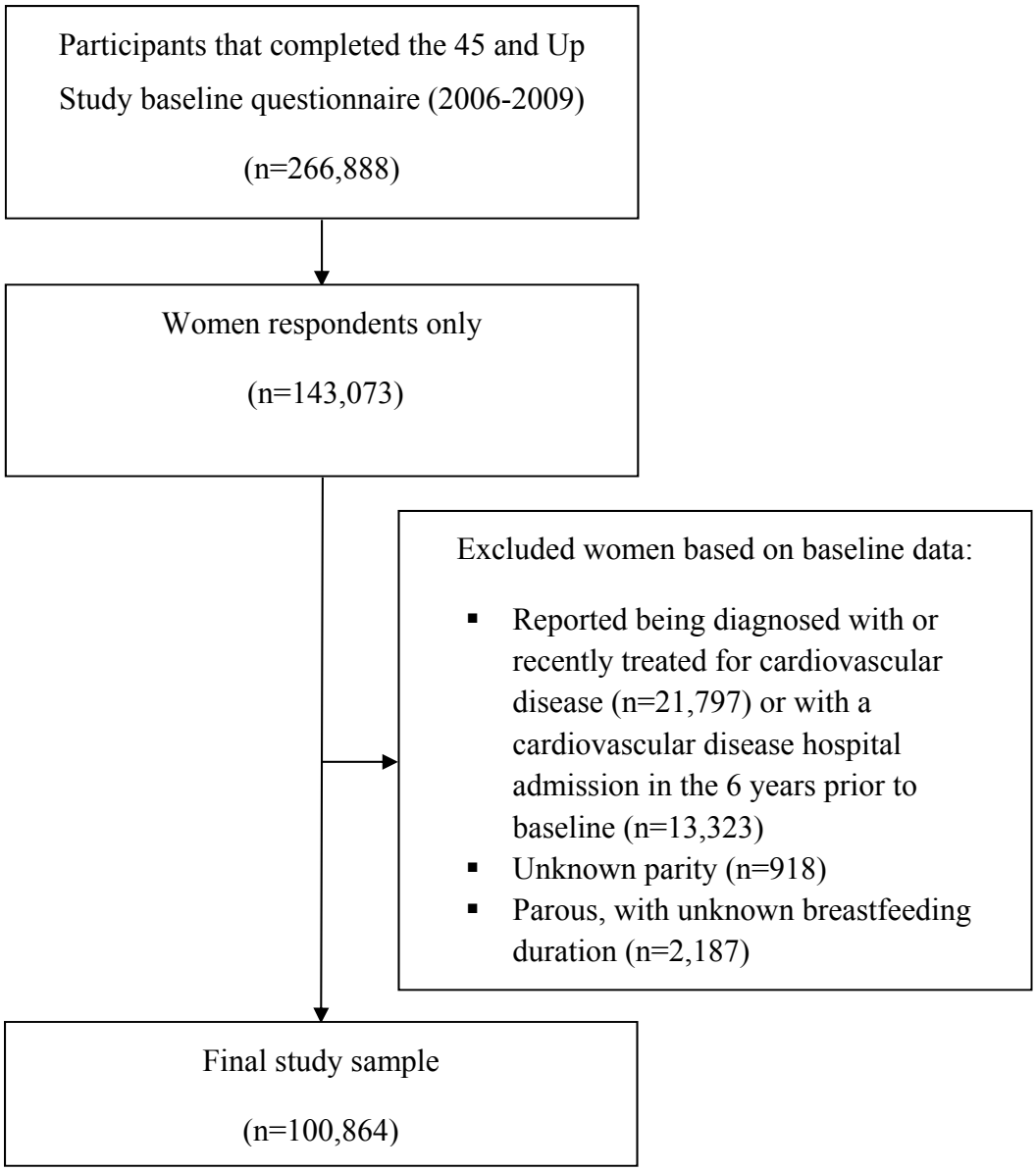

Fig. 1. Participant flow chart

Table 1. Baseline socio-demographic characteristics and parity of parous women (n=100,864) in the 45 and Up Study by breastfeeding history and average breastfeeding duration per child.*

Variables	**Breastfeeding history**			**Average breastfeeding duration per child†**			
	Never breastfed	**Ever breastfed**	**P-value‡**	**>0 to 6 months**	**>6 to 12 months**	**>12 months**	**P-value§**
Number of subjects (%)	12,517 (12.4)	88,347 (87.6)		56,049 (63.4)	24,549 (27.8)	7,749 (8.8)	
Age group (%)							
45 to 54 years	26.5	37.7	<0.0001	29.5	47.3	66.9	<0.0001
55 to 64 years	42.7	34.0		36.5	29.7	28.9	
≥65 years	30.8	28.3		34.0	23.0	4.2	
Mean (SD) age for first child (years)	24.3 (5.15)	25.1 (4.89)	<0.0001	24.3 (4.66)	26.0 (4.74)	28.1 (5.29)	<0.0001

Mean (SD) age for last child (years)	28.9 (5.24)	30.6 (4.96)	<0.0001	29.8 (4.93)	31.6 (4.64)	33.4 (4.7)	<0.0001
Parity							
Mean (SD) parity (number of births)	2.4 (1.13)	2.7 (1.18)	<0.0001	2.8 (1.2)	2.8 (1.15)	2.6 (1.13)	<0.0001
1 child (%)	19.0	8.7	<0.0001	16.7	9.5	3.9	<0.0001
2 children (%)	43.7	39.8		47.7	46.4	41.5	
3 children (%)	23.8	31.2		24.3	29.8	35.0	
≥4 children (%)	13.5	20.3		11.3	14.3	19.6	
Country of birth (%)							
Australia	72.0	77.3	<0.0001	74.0	76.1	79.7	<0.0001
Other	28.0	22.7		26.0	23.9	20.3	
Highest education[‖] (%)							
University and higher	11.1	23.8	<0.0001	16.3	21.3	27.0	<0.0001

High school/trade apprenticeship/ certificate/diploma	33.3	38.4		37.1	37.9	39.4	
≤10 years	55.6	37.8		46.6	40.8	33.6	
Marital status[¶] *(%)*							
Married/living with a partner	72.7	75.8	<0.0001	74.6	75.0	76.7	<0.0001
Single/divorced/separated/ widowed	27.3	24.2		25.4	25.0	23.3	
Socioeconomic status[**] *(SEIFA-IRSD) (%)*							
Quintile 1 (most disadvantaged)	23.2	19.7	<0.0001	21.1	19.8	18.2	<0.0001
Quintile 2	20.3	19.5		20.1	18.8	19.0	
Quintile 3	22.5	21.4		21.8	21.2	20.7	
Quintile 4	19.0	19.6		19.7	19.6	20.0	

Quintile 5 (least disadvantaged)	15.0	19.8	17.3	20.5	22.0

SD=standard deviation; SEIFA-IRSD=Socio-Economic Indexes For Area - Index of Relative Socio-Economic Disadvantage.

* Data are presented as means (SD) or percentages.

† Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

‡ Based on chi-square test for categorical variables and student t-test for continuous variables.

§ Based on chi-square test for categorical variables and F statistics from ANOVA for continuous variables.

‖ 1,325 missing.

¶ 268 missing.

** 66 missing.

Table 2. Hazard ratios and 95% confidence intervals for the incidence of CVD hospitalisation and mortality in parous women by average breastfeeding duration per child.*

Average breastfeeding duration per child[a]	**No. of persons, n**	**Person-years from baseline**	**No. of incident cases/deaths**	**Model 1**† **(95% CI)**	**Model 2**‡ **(95% CI)**	**Model 3**§ **(95% CI)**	**Model 4**‖ **(95% CI)**
CVD hospitalisation							
Never breastfed	12,517	76,164	527	Reference	Reference	Reference	Reference
>0-6 months	56,049	342,296	2076	0.82 (0.74, 0.91)	0.84 (0.76, 0.93)	0.86 (0.77, 0.95)	0.86 (0.78, 0.96)
>6-12 months	24,549	150,489	708	0.77 (0.68, 0.87)	0.79 (0.70, 0.89)	0.84 (0.74, 0.96)	0.85 (0.75, 0.97)
>12 months	7,749	47,911	117	0.80	0.84	0.89	0.89

				(0.65, 0.99)	(0.68, 1.04)	(0.71, 1.12)	(0.71, 1.12)
CVD mortality							
Never breastfed	12,517	71,730	66	Reference	Reference	Reference	Reference
>0-6 months	56,049	321,326	247	0.69 (0.53, 0.92)	0.74 (0.56, 0.98)	0.69 (0.51, 0.94)	0.69 (0.51, 0.94)
>6-12 months	25,549	140,605	96	0.53 (0.38, 0.73)	0.56 (0.40, 0.79)	0.59 (0.41, 0.85)	0.59 (0.41, 0.84)
≥12 months	7,749	44,453	9	0.76 (0.36, 1.61)	0.80 (0.38, 1.69)	0.70 (0.30, 1.65)	0.67 (0.28, 1.57)

CI= confidence interval, CVD=cardiovascular disease.

[*] Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

[†] Model 1 was unadjusted.

‡ Model 2 was adjusted for parity (number of children) and socio-demographic characteristics (age, country of birth, educational level, marital status, area-level socio-economic status).

§ Model 3 was further adjusted for lifestyle factors: body mass index, smoking status, alcohol intake, physical activity.

‖ Model 4 was additionally adjusted for medical and reproductive covariates: multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

Supplementary Table 1. Baseline lifestyle, medical and reproductive characteristics of parous women (n=100,864) in the 45 and Up Study by breastfeeding history and average breastfeeding duration per child.[*]

Variables	**Breastfeeding history**			**Average breastfeeding duration per child**[†]			
	Never breastfed	**Ever breastfed**	**P-value**[‡]	**>0-6 months**	**>6-12 months**	**>12 months**	**P-value**[§]
Number of subjects (%)	12,517 (12.4)	88,347 (87.6)		56,049 (63.4)	24,549 (27.8)	7,749 (8.8)	
BMI category[‖] *(%)*							
Underweight/healthy weight (≤18.5 to <25.0 kg/m^2)	38.8	45.2	<0.0001	42.6	48.8	52.7	<0.0001
Overweight (25.0 to <30.0 kg/m^2)	33.0	33.4		23.2	18.5	17.5	
Obese (≥30.0 kg/m^2)	28.2	21.4		24.2	21.2	19.6	

Mean (SD) physical activity time (minutes/week)	599 (711)	602 (650)	0.68	601 (662)	601 (629)	606 (627)	0.90
Physical activity category[¶] (%)							
<150 minutes/week	26.8	21.2	<0.0001	22.8	19.0	16.5	<0.0001
150 to 299 minutes/week	14.8	16.0		15.6	16.4	18.1	
≥300 minutes/week	58.4	62.8		61.6	64.6	65.4	
Smoking status[**] (%)							
Never smoker	60.5	65.5	<0.0001	63.9	69.0	65.6	<0.0001
Past regular smoker	28.8	28.0		28.7	26.1	29.1	
Current smoker	10.6	6.5		7.4	4.9	5.3	
Current alcohol intake (drinks/week)[††] (%)							
≤14 drinks/week	90.5	89.7	<0.0001	89.3	90.3	91.1	<0.0001
>14 drinks/week	9.5	10.3		10.7	9.7	8.9	

Healthy lifestyle index[‡‡]							
Healthy	72.7	63.5	<0.0001	66.6	59.1	56.5	<0.0001
Not healthy	27.3	36.5		33.4	40.9	43.5	
Current use of multivitamins (%)	25.5	30.1	<0.0001	29.2	30.6	34.6	<0.0001
Current use of omega 3 or fish oil (%)[§§]	34.2	37.0	<0.0001	38.0	35.5	34.8	<0.0001
Current use of aspirin[‖‖] (%)	14.7	13.3	<0.0001	14.8	11.5	7.6	<0.0001
History of oral contraceptive use[¶¶] (%)	80.1	83.6	<0.0001	83.0	83.4	89.3	<0.0001
Family history of cardiovascular disease[***] (%)	58.1	57.9	0.78	59.0	55.9	56.3	<0.0001
Family history of hypertension[†††] (%)	54.7	56.1	0.004	55.4	56.4	60.0	<0.0001

Family history of diabetes‡‡‡ (%)	27.0	24.0	<0.0001	24.5	23.1	24.2	<0.0001
Self-reported hypertension/ recent treatment for hypertension (%)	24.9	20.5	<0.0001	23.2	17.6	10.6	<0.0001
Self-reported diabetes/ recent treatment for diabetes (%)	9.8	5.6	<0.0001	6.4	4.6	3.5	<0.0001

BMI= body mass index; SD=standard deviation.

* Data are presented as means (SD) or percentages.

† Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

‡ Based on chi-square test for categorical variables and student t-test for continuous variables.

§ Based on chi-square test for categorical variables and F statistics from ANOVA for continuous variables.

‖ 8,273 missing.

¶ 1,370 missing.

** 5 missing.

†† 2,091 missing.

‡‡ 15,623 missing. Based on six lifestyle risk factors scored individually as either healthy (score=1) or not healthy (score=0), as follows: body mass index (<25 kg/m^2=score 1, ≥25 kg/m^2=score 0), physical activity level (<150 min/week=score 0; ≥150 min/week=score 1), smoking status (past/current smoker=score 0; never smoker=score 1), alcohol intake (≤14 drinks/week=score 0; >14 drinks/week=score 1), sleep (>7-<9 hours/day=score 0; <7 hours/day or >9 hours/day=score 1), fruit and vegetable intake (<2 serves of fruit/day and <3 serves of fruit/day=score 0; ≥2 serves of fruit/day and ≥3 serves of vegetables/day=score 1). Based on the sum of these scores, the healthy lifestyle index was dichotomised as either healthy (sum of scores=5-6) or not healthy (sum of scores=0-4).

§§ 1 missing.

|||| 6 missing.

¶¶ 1,571 missing.

*** 9 missing.

††† 9 missing.

‡‡‡ 9 missing.

Supplementary Table 2. Hazard ratios and 95% confidence intervals for the incidence of CVD hospitalisation and mortality in parous women, by breastfeeding history.

Breastfeeding history	**No. of persons, n**	**Person-years from baseline**	**No. of incident cases/deaths**	**Model 1*** **(95% CI)**	**Model 2†** **(95% CI)**	**Model 3‡** **(95% CI)**	**Model 4§** **(95% CI)**
CVD hospitalisation							
Parous, Never breastfed	12,517	76,164	527	Reference	Reference	Reference	Reference
Parous, Ever breastfed	88,347	540 696	2,901	0.81 (0.73,0.89)	0.83 (0.75,0.91)	0.85 (0.77,0.95)	0.86 (0.78,0.96)
P-value‖				<0.001	<0.001	0.003	0.005
CVD mortality							

Parous, Never breastfed	12,517	71 730	66	Reference	Reference	Reference	Reference
Parous, Ever breastfed	88,347	506,383	352	0.65 (0.49,0.85)	0.69 (0.52,0.91)	0.66 (0.50,0.89)	0.66 (0.49,0.89)
P-value[‖]				0.002	0.008	0.006	0.006

CI= confidence interval, CVD=cardiovascular disease.

[*] Model 1 was unadjusted.

[†] Model 2 was adjusted for parity (number of children) and socio-demographic characteristics (age, country of birth, educational level, marital status, area-level socio-economic status).

[‡] Model 3 was further adjusted for lifestyle factors: body mass index, smoking status, alcohol intake, physical activity.

[§] Model 4 was additionally adjusted for medical and reproductive covariates: multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

[‖] From Type 3 Wald chi-square test.

Supplementary Table 3. Adjusted hazard ratios and 95% confidence intervals for associations between average breastfeeding duration per child and the incidence of CVD hospitalisation and mortality in parous women, stratified by highest educational level.

Highest educational level	**Average breastfeeding duration per child**	**No. of persons, n**	**Person-years from baseline (from birth of first child)**	**No. of incident cases/deaths**	**Multivariate-adjusted[*] (95% CI)**
CVD hospitalisation					
University and higher	**Never breastfed**	1,362	8,364	38	Reference
	>0-6 months	9,915	61,035	239	0.90 (0.62, 1.30)
	>6-12 months	7,462	46,238	111	0.81 (0.55, 1.20)
	>12 months	3,383	21,027	39	0.92 (0.57, 1.48)

High school/trade apprenticeship/ certificate/diploma	**Never breastfed**	4,089	24,986	152	Reference
	>0-6 months	20,696	126,795	680	0.89 (0.74, 1.08)
	>6-12 months	9,730	59,834	238	0.83 (0.66, 1.03)
	>12 months	3,101	19,141	49	0.94 (0.66, 1.33)
≤10 years	**Never breastfed**	6,830	41,444	320	Reference
	>0-6 months	24,669	149,919	1,113	0.85 (0.74, 0.97)
	>6-12 months	7,098	42,878	348	0.90 (0.76, 1.07)
	>12 months	1,204	7,374	25	0.75 (0.48, 1.18)
CVD mortality					

University and higher	**Never breastfed**	1,362	7,808	<5	Reference
	>0-6 months	9,915	56,884	20	0.66 (0.19, 2.26)
	>6-12 months	7,462	42,910	<5	0.28 (0.06, 1.27)
	>12 months	3,383	19,477	0	-
High school/trade apprenticeship/ certificate/diploma	**Never breastfed**	4,089	23,470	20	Reference
	>0-6 months	20,696	118,767	63	0.51 (0.30, 0.87)
	>6-12 months	9,730	55,765	32	0.65 (0.36, 1.17)
	>12 months	3,101	17,769	<5	0.26 (0.03, 1.94)
≤10 years	**Never breastfed**	6,830	39,118	41	Reference

	>0-6 months	24,669	141,360	154	0.77 (0.53, 1.13)
	>6-12 months	7,098	40,484	51	0.52 (0.33, 0.84)
	>12 months	1,204	6,860	6	1.06 (0.37, 3.02)

CI= confidence interval, CVD=cardiovascular disease.

* Adjusted for age, country of birth, educational level, marital status, area-level socio-economic status, body mass index, smoking status, alcohol intake, physical activity, multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, number of children, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

Supplementary Table 4. Adjusted hazard ratios and 95% confidence intervals for associations between average breastfeeding duration per child and the incidence of CVD hospitalisation and mortality in parous women, stratified by the healthy lifestyle index.

Healthy lifestyle index*	**Average breastfeeding duration per child†**	**No. of persons, n**	**Person-years from baseline (from birth of first child)**	**No. of incident cases/deaths**	**Multivariate-adjusted‡ (95% CI)**
CVD hospitalisation					
Healthy	**Never breastfed**	2,812	17,354	77	Reference
	>0-6 months	15,724	96,582	490	1.11 (0.87, 1.42)
	>6-12 months	8,652	53,261	197	1.01 (0.77, 1.32)
	>12 months	2,948	18,230	37	1.15 (0.77, 1.72)

Not healthy	**Never breastfed**	7,487	45,413	345	Reference
	>0-6 months	31,297	191,309	1,157	0.79 (0.70, 0.90)
	>6-12 months	12,485	76,576	371	0.80 (0.68, 0.93)
	>12 months	3,836	23,718	61	0.82 (0.62, 1.09)
CVD mortality					
Healthy	**Never breastfed**	2,812	16,201	10	Reference
	>0-6 months	15,724	90,369	43	0.68 (0.34, 1.36)
	>6-12 months	8,652	49,616	15	0.40 (0.18, 0.90)
	>12 months	2,948	16,894	<5	0.93 (0.20, 4.31)

Not healthy	**Never breastfed**	7,487	42,853	39	Reference
	>0-6 months	31,297	179,631	130	0.68 (0.47, 0.99)
	>6-12 months	12,485	71,602	48	0.59 (0.38, 0.92)
	>12 months	3,836	22,019	<5	0.57 (0.18, 1.88)

CI= confidence interval, CVD=cardiovascular disease.

* Based on six lifestyle risk factors scored individually as either healthy (score=1) or not healthy (score=0): body mass index (<25 kg/m^2=score 1, ≥25 kg/m^2=score 0), physical activity level (<150 min/week=score 0; ≥150 min/week=score 1), smoking status (past/current smoker=score 0; never smoker=score 1), alcohol intake (≤14 drinks/week=score 0; >14 drinks/week=score 1), sleep (>7-<9 hours/day=score 0; <7 hours/day or >9 hours/day=score 1), fruit and vegetable intake (<2 serves of fruit/day and <3 serves of fruit/day=score 0; ≥2 serves of fruit/day and ≥3 serves of vegetables/day=score 1). Based on the sum of these scores, the healthy lifestyle index was dichotomised as either healthy (sum of scores=5-6) or not healthy (sum of scores=0-4).

† Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

‡ Adjusted for age, country of birth, educational level, marital status, area-level socio-economic status, multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, number of children, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

Supplementary Table 5. Summary of recent prospective/case-cohort studies that have examined the association between breastfeeding history/duration and CVD outcomes.

First author (year)	Country and cohort designation	Participants	Mean follow-up (years)	Outcome assessment	Breastfeeding comparison categories	Adjusted HR (95% CI) by breastfeeding history/ duration	Covariates
Merritt et al. (2015) [1]	10 European countries, EPIC study	322,972 parous women without a history of MI/heart attack, angina, stroke or cancer; 25-70 years	12.9	Mortality from:			Education level, BMI, physical activity, smoking status/intensity and duration, menopausal status
				Circulatory disease	Never	Reference	
					Ever	0.80 (0.70, 0.91)	
				Cerebrovascular disease	Never	Reference	
					Ever	0.94 (0.74, 1.21)	
				IHD	Never	Reference	
					Ever	0.69 (0.54, 0.87)	

Peters et al. (2016) [2]	10 European countries, case-cohort study nested within EPIC study	Parous women without a history of IHD or stroke; mean age=52.7 (SD: 9.1) years; n=8,044 for analyses comparing never vs. ever breastfeeding and n=8,012 for analyses involving breastfeeding duration	11	Incidence of first-time non-fatal/fatal IHD event	Never Ever Average breastfeeding duration/child Never >0-<1 month ≥1-<3 months ≥3-<6 months ≥6 months	Reference 0.71 (0.52, 0.98) 1.00 (0.73, 1.37) 0.77 (0.63, 0.94) 0.69 (0.61, 0.78) 0.67 (0.57, 0.77) 0.67 (0.56, 0.80)	Study centre, age, education level, BMI, smoking status, number of live births, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus
Peters et al. (2017) [3]	10 diverse regions in China,	289,573 without a history of IHD or stroke; 30-79 years	8.1 (median)	Incidence of: All CVD	Never Ever	1.00 (0.95, 1.05) 0.96 (0.95, 0.97)	Education level, household income, BMI, physical activity, smoking status, alcohol intake,

China Kadoorie Biobank		Each additional 6 months/child*	0.98 (0.97, 0.99)	systolic blood pressure, history of hypertension, history of diabetes mellitus
	Major CVD			
		Never	1.00 (0.92, 1.09)	
		Ever	0.88 (0.87, 0.90)	
		Each additional 6 months/child*	0.97 (0.96, 0.99)	
	Fatal CVD			
		Never	1.00 (0.77, 1.29)	
		Ever	0.90 (0.87, 0.94)	
		Each additional 6 months/child*	0.98 (0.95, 1.01)	
	Stroke			
		Never	1.00 (0.93, 1.08)	
		Ever	0.92 (0.90, 0.93)	

		Each additional 6 months/child*	0.97 (0.96, 0.98)
	Haemorrhagic stroke		
		Never	1.00 (0.77, 1.31)
		Ever	0.84 (0.81, 0.88)
		Each additional 6 months/child*	0.99 (0.96, 1.03)
	Ischemic stroke		
		Never	1.00 (0.91, 1.09)
		Ever	0.88 (0.86, 0.90)
		Each additional 6 months/child*	0.97 (0.95, 0.98)
	IHD		
		Never	1.00 (0.92, 1.09)
		Ever	0.91 (0.89, 0.93)

	Each additional 6 months/child*	0.96 (0.95, 0.98)

Abbreviations: BMI=body mass index, CVD=cardiovascular disease, EPIC=European Investigation into Cancer and Nutrition prospective cohort study, HDL=high-density lipoprotein, HR=hazard ratio, IHD=ischaemic heart disease, MI=myocardial infarction, SD=standard deviation.

* Among parous women that had ever breastfed.

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7.5 CONCLUDING SUMMARY FOR THIS CHAPTER AND KNOWLEDGE GAINED FROM THIS STUDY

To our knowledge, this was the first prospective cohort study in Australia to examine the association between breastfeeding and CVD-related hospitalisation and mortality among women. Breastfeeding was associated with a lower risk of CVD hospitalisation and mortality, an association that was consistent across different lifestyle and education categories. This study contributes evidence that breastfeeding may provide long-term benefits for cardiovascular health in parous women and may be used as an additional prevention strategy for CVD.

CHAPTER EIGHT: Discussion

This thesis examined innovative aspects of cardiovascular risk among a large cohort of middle-aged and older Australian men and women. This chapter discusses the overall significance of findings from studies presented in **Chapters 3 to 7** and **Appendix 1**, the implications for policy, the strengths and limitations of this research, and some directions for future research.

8.1 SIGNIFICANCE OF THE FINDINGS

The overall significance of this research should be viewed in light of 1) its potential to inform gender-specific, CVD prevention strategies involving lifestyle risk factors, and 2) both its methodological strengths and limitations (presented in section 8.3).

Considering that CVD is the leading cause of death worldwide in both men and women, growing knowledge about emerging lifestyle risk factors, and the lack of gender-specific CVD research, findings from this doctoral research may inform gender-specific prevention strategies in middle-aged and older adults. Findings presented in this thesis contribute to the evidence base. Firstly, emerging and lesser known lifestyle risk factors for CVD were examined, such as raw vegetable consumption, sedentary behaviour and psychological distress. Secondly, the joint influence of lifestyle risk factors which rarely occur in isolation was explored in relation to the development of type 2 diabetes and hypertension, both major cardiovascular risk factors. Thirdly, potential gender differences and behaviours specific to women such as breastfeeding, an important maternal behaviour with many potential health benefits, were examined.

To help gain an overall picture of the significance of findings in this thesis, **Table 8.1** summarises the main findings, including any observed gender differences, from each of the five studies included in this thesis, along with their individual significance. To summarise findings in this large cohort of middle-aged and older Australians succinctly, the first study (**Chapter 3**) found that the consumption of fruit and vegetables, considered separately or combined, was inversely related with all-cause mortality. However, additional research is required to examine the effects of raw versus cooked vegetable consumption as well as confirm observed gender differences including a more protective effect of fruit and vegetable consumption in women. In the second

Table 8.1. Summary and significance of findings from five studies presented in this thesis.

Thesis chapter	Manuscript title	Main findings	Gender differences	Significance of findings
3	Fruit and vegetable consumption and ACM	Fruit and vegetable consumption, considered combined or separate, was inversely related to ACM. Further studies needed to explore the effects of raw versus cooked vegetables.	Combined consumption of fruit and vegetables, and separate consumption of vegetables, were inversely related with ACM in women, but not in men.	First prospective cohort study to examine these associations in Australia. Findings contribute to the evidence base for the protective effects of fruit and vegetables. Findings support Australian dietary guidelines. Additional studies needed to explore the effects of raw versus cooked vegetables. Additional studies needed to confirm observed differences between men and women.
4	Incident T2DM in a large Australian cohort study: Does PA or sitting time alter the risk associated with BMI?	High levels of PA and/or low levels of sitting did not offset the risk of T2DM associated with overweight/obesity.	A gender-specific analysis (results presented in **Appendix 1**) was conducted as an addition to this published manuscript. The main findings remained essentially the same in separate analyses in men and women.	First prospective study to examine whether PA and sitting time can attenuate the risk of developing T2DM associated with BMI. Findings contribute to the evidence base that BMI is a more important risk factor than PA for T2DM prevention. Further studies needed to examine whether sitting time is associated with the incidence of T2DM.

				Maintaining a healthy weight, by adopting healthy lifestyle behaviours, is important for T2DM prevention. No obvious differences between men and women.
5	Association between lifestyle risk factors and incident hypertension among middle-aged and older Australians	Being overweight/obese, a high alcohol consumption, low PA levels and being a current smoker were associated with a higher incidence of HT. There was no obvious association between psychological distress and incident hypertension. Positive association between the number of high-risk lifestyle factors and odds of developing hypertension. This association was stronger in middle-aged than in older adults.	Except for smoking, findings relating to individual lifestyle risk factors and HT in the overall sample were similar in men and women. A high-risk lifestyle was more detrimental for developing HT in men than in women, particularly in middle-aged men.	First prospective study to compare associations in men and women. Findings contribute to the evidence base for the importance of adopting healthy lifestyle behaviours to prevent HT. Although further studies are needed, middle-aged adults, particularly men, were identified as at higher risk. Findings in parous women contribute to the evidence base for the protective effects of breastfeeding in relation to HT. Further studies needed to examine the association between mental health and incident HT.
6	Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review	Significant protective effects of breastfeeding were reported in most studies included in this systematic review. Breastfeeding was associated with both short- and long-term maternal cardiovascular health risk	Study specific to women.	First systematic review of the association between breastfeeding and metabolic syndrome, HT and CVD. Findings support health promotion efforts to increase breastfeeding. Further longitudinal studies needed.

		factors/outcomes. Evidence most convincing for HT. Evidence limited by small number of longitudinal studies.		
7	Breastfeeding and CVD hospitalisation and mortality in parous women: Evidence from a large Australian cohort study	Breastfeeding was associated with lower risk of CVD hospitalisation and mortality in parous women. Breastfeeding may offer long-term benefits for maternal cardiovascular health. Associations were mostly consistent across different education and lifestyle categories.	Study specific to women.	First prospective cohort study to examine these associations in Australia. Findings contribute to the growing evidence base for the protective effects of breastfeeding for maternal cardiovascular health. Breastfeeding may provide additional health benefits to women that breastfeed. Breastfeeding may be used as an additional strategy for CVD prevention.

Abbreviations: ACM=all-cause mortality; BMI=body mass index; CVD=cardiovascular disease; HT=hypertension; PA=physical activity, T2DM=type 2 diabetes mellitus.

study presented in this thesis (**Chapter 4**), body mass index was more strongly associated with the risk of developing of type 2 diabetes than physical activity levels or sitting time. In addition, engaging in high levels of physical activity and spending little time sitting did not attenuate the risk of developing type 2 diabetes associated with being overweight/obese in both men and women, as described in **Tables 1 to 6** in **Appendix 1**. There was no obvious association between sitting time and the risk of type 2 diabetes. In the third study (**Chapter 5**), a high body mass index, high alcohol intake and low physical activity were all associated with a higher risk of developing hypertension in both men and women. There was no significant association between high psychological distress and incident hypertension. Having an increasing number of lifestyle risk factors was associated with an increasing risk of hypertension in both men and women. This association was stronger in middle-aged than older adults, particularly in men. In the fourth study (**Chapter 6**), a systematic review provided evidence for an association between breastfeeding and both short- and long-term cardiovascular risk factors and outcomes. However, a lack of longitudinal studies was identified as a research gap. The fifth study (**Chapter 7**) addressed this research gap by examining the longitudinal association between breastfeeding and cardiovascular disease-related hospitalisation and mortality and confirmed that breastfeeding was associated with a lower risk of CVD hospitalisation and mortality.

Four of the five studies presented in this thesis have been published (corresponding to **Chapters 3-6**) and one is currently in press (**Chapter 7**). Several of these studies were among the first in Australia (**Chapters 3, 7**) or worldwide (**Chapters 4-6**) to explore these associations and potential gender differences (**Chapters 3-5, Appendix 1**) in a large cohort, providing unique contributions to the evidence base. Most cardiovascular risk factors examined were leading lifestyle and metabolic risk factors for global disease burden or disability.[1-3] Findings reaffirmed Australian recommendations for fruit and vegetable intake, as well as current guidelines for physical activity, alcohol intake, and infant breastfeeding. Studies examining the separate or combined influence of lifestyle risk factors reinforced the importance of adopting overall healthy lifestyle behaviours to reduce cardiovascular risk factors, such as type 2 diabetes and hypertension, as well as identified the relatively stronger lifestyle risk factors, among middle-aged and older men and women. Findings confirmed that adhering to a healthy lifestyle can substantially improve CVD risk in the middle-aged and older population, which can lead to improving longer-term health outcomes. In addition, this thesis offers preliminary evidence that differences between men and

women may exist in relation to different lifestyle risk behaviours and CVD risk factors, which are worth further exploring. The need for more gender-specific analysis in CVD prevention research has been expressed by several health bodies, including the American Heart Association which has strived to develop guidelines for the prevention of CVD in women, albeit with studies predominantly involving men.[4] Findings from this thesis may be conducive to future gender-specific CVD research which can inform future gender-specific guidelines for the prevention of CVD.

Although this research project reaffirmed the importance of reducing traditional lifestyle risk factors for CVD prevention, the evidence for an association between less well established risk factors, such as raw vegetable consumption, sitting time, poor mental health and CVD risk factors or outcomes, was less clear. However, they contribute valuable information that should be considered in weighing the overall evidence and developing CVD prevention policies. Indeed, the study about fruit and vegetable consumption and all-cause mortality (**Chapter 3**) has been included in two recent meta-analyses and systematic reviews published in high-ranking journals, which support public health recommendations to promote fruit and vegetable intake for the prevention of CVD and premature death.[5,6] The study examining the separate and combined influence of body mass index, physical activity and sitting time on incident type 2 diabetes (**Chapter 4**) has been included and cited in the most recent American Physical Activity Guidelines Advisory Committee Scientific Report.[7]

In contrast to other innovative risk factors examined in this thesis, breastfeeding emerged as an additional strategy by which parous women may lower their risk of CVD. The systematic review (**Chapter 6**) contributed to women's health research by synthesising the current evidence about the relation between breastfeeding and a range of maternal cardiovascular risk factors and outcomes. Conducting this systematic review was important to evaluate whether breastfeeding could be a modifiable risk factor for CVD and whether it provided long-term beneficial effects for maternal cardiovascular health. The study relating to breastfeeding (**Chapter 7**) aimed to address a research gap identified in the systematic review, providing additional longitudinal evidence for the long-term protective effects of breastfeeding for maternal cardiovascular health.

Overall, this thesis contributes important public health findings that are of substantial significance to men and women in the population, health care providers, and policy makers. It has

recently been estimated that Australia's spending on preventative health is approximately $2 billion per year or 1.34% of all health expenditure, and a joint campaign led by public health, not-for-profit, research and advocacy bodies have advocated that more spending should go towards preventive health.[8] Findings from this thesis confirm the importance of focusing on traditional and innovative aspects of cardiovascular risk for the prevention of CVD in both middle-aged and older men and women, and developing prevention strategies that are informed by research. With increased pressure on the Australian healthcare system stemming from a growing ageing population, and given the preventable nature of lifestyle-related NCDs, the Australian government needs to upscale its investment in prevention research and programs.

8.2 IMPLICATIONS FOR POLICY

The findings from the collection of studies presented in this thesis have several implications for public health programs and policy. One of the implications for policy is the importance of incorporating growing evidence about innovative aspects of cardiovascular risk in the development of prevention strategies for CVD. While the evidence for certain lesser known risk factors, such as sedentary behaviour and psychological distress in relation to incident type 2 diabetes and hypertension respectively, was inconclusive and requires further research, more solid evidence was presented in support of breastfeeding as a supplementary strategy by which parous women could reduce their risk of CVD. Developing policies that support women to initiate and continue breastfeeding will not only benefit the health of children, but also the health of mothers and potentially provide added cardiovascular health benefits. Currently, 96% of Australian women initiate breastfeeding after birth. However, only 15 to 25% will exclusively breastfeed their babies until 6 months of age.[9] Policies should be implemented to help reduce barriers for breastfeeding and promote breastfeeding in various settings, such as providing continuity of care between health care facilities and the broader community, and facilitating breastfeeding in public places and in the workplace.[10,11] The Australian National Breastfeeding Strategy 2010-15 provided a framework for governments to take action in collaboration with the community sector to protect, promote, and support breastfeeding as well as monitor activities at the state, territory and national levels.[10] A national breastfeeding strategy for 2018 and beyond, is in the process of being developed by the Australian Government Department of Health, which could be informed by research stemming from this thesis.

Exploring the effects of multiple lifestyle risk factors on major cardiovascular risk factors such as diabetes and hypertension, provided insight on the joint and relative influence of examined lifestyle risk factors. This novel approach may not only guide prevention strategies for specific cardiovascular risk factors but also inform strategies that simultaneously address lifestyle correlates of CVD risk factors. Strategies aimed at risk reduction may be more efficient and cost-effective in preventing premature deaths from CVD by targeting multiple risk factors rather than separate ones.[12] In addition, targeting common risk factors, an approach adopted in the *2017 National Strategic Framework for Chronic Conditions* and by the WHO in its *Global Action Plan for the Prevention and Control of NCDs 2013-2020*,[13,14] can also help prevent deaths from other NCDs.

This thesis focused on prevention research in middle-aged and older Australians because a considerable proportion of deaths due to CVD occur prematurely and are substantially preventable. Findings from this thesis confirmed the importance of lifestyle factors in the middle-age population with the potential to reduce health care burden later in life. Intervening during middle age is essential given the higher life expectancy of Australians and the projection that the proportion of Australians aged 65 years and over will be 22% in 2057.[15] A growing ageing population will provide increased pressure on the health system, including higher health care costs, emphasising the urgency of investing in cost-effective prevention strategies for middle-aged men and women.

A gender-specific approach to both research and policy is needed to help develop programs and policies that address health issues that are specific to women and men. Both a National Women's Health Policy and a National Men's Health Policy were developed in 2010 with the aim to improve the health of women and men in the next 10 to 20 years.[16,17] One key health priority area identified in these policies was chronic disease prevention by targeting lifestyle risk factors. While these national policies are a promising start, a greater gender focus in research and policy is still being advocated for by the Public Health Association of Australia as evidence-based policies on gender and health are still needed at all government levels.[18] The gender focus adopted in this thesis may open doors for further gender-specific prevention research that has the potential to influence future public health guidelines and policy frameworks with a gender focus.

In 2017, Australia put in place a *National Strategic Framework for Chronic Conditions*.[13] However, a national implementation plan or strategy that specifically addresses CVD is currently

lacking. In its 2017-2018 federal budget submission, the Heart Foundation advocated for the development of a national heart and stroke strategy that would be integral to the *National Strategic Framework for Chronic Conditions*.[19] Such a strategy could help develop more CVD prevention-based policies that have a major impact on CVD prevention and lowering health care burden.

8.3 METHODOLOGICAL STRENGTHS AND LIMITATIONS

One of the main strengths of this thesis was that research questions were examined using a large population-based cohort study on healthy ageing. This type of observational study helped to establish a temporal framework for associations examined in this thesis which encompassed some of Bradford Hill's criteria including: a temporal sequence, biological plausibility, coherence and consistency.[20] In addition, a comprehensive range of sociodemographic and health-related longitudinal data were available for men and women, including reproductive factors that are unique to women. Questionnaire data were linked to population health databases, providing an optimal research setting for exploring associations over time between lifestyle behaviours and CVD risk factors/outcomes. These methodological strengths lend support to findings from this thesis which add to the evidence base for the importance of healthy lifestyle behaviours for improved CVD-related outcomes.

There were several methodological limitations. Sample size calculations were not conducted a priori. The follow-up times were relatively short, potentially limiting the extent of longitudinal associations that were observed. As the 45 and Up Study is a large longitudinal cohort study, questionnaires were administered to lower respondent burden and data were mainly self-reported. Response bias could have been introduced and could potentially differ by gender. It should be noted that a previous study comparing participants from the 45 and Up Study with a representative sample from the New South Wales Population Health Survey, reported that exposure-outcome associations had similar estimates although risk factor prevalence differed between both samples.[21] In addition, most measures used were validated either among the 45 and Up participants or in other samples. Fruit and vegetable consumption was assessed using established measures. However, controlling for other aspects of dietary intake was difficult because of limitations in the brief dietary questions asked. There was also a possibility for residual confounding in longitudinal

studies, which was minimised by adjusting for a range of sociodemographic and health-related covariates and conducting sensitivity analyses to test the robustness of findings.

8.4 DIRECTIONS FOR FUTURE RESEARCH

This collection of peer-reviewed studies provides an initial but important investigation of innovative aspects of CVD that is relevant to middle-aged and older men and women in the population, health care providers, and policy makers. Future research can help further elucidate the role of innovative cardiovascular risk factors examined in this thesis. High-quality prospective cohort studies that include large sample sizes, validated measures of exposures and outcomes, long-term follow-up measures, a range of sociodemographic, medical and lifestyle data, as well as good linkage to hospitalisation and mortality data can provide excellent research settings to explore temporal associations between cardiovascular risk factors and outcomes. Although fruit and vegetable consumption was found to be beneficial, future studies should further explore whether different preparation methods, such as raw vs. cooked vegetables have differential effects on cardiovascular health. Additional research is also needed to examine the roles of sedentary behaviour and poor mental health in relation to CVD as findings from this thesis did not provide conclusive evidence. The effects of specific combinations of lifestyle risk factors, including emerging ones, on CVD risk factors/outcomes is another key area for future research. There is a range of combinations that has not been explored and further research could provide additional insight on the joint and relative influence of lifestyle risk factors on CVD and guide prevention strategies among the middle-aged and older population.

While there is more CVD research being conducted in women, there is still a need for increased representation of women in studies and research that acknowledges the importance of considering risk factors that are unique to women. This thesis presented evidence for an association between breastfeeding and cardiovascular risk factors and outcomes, even across different levels of education and healthy lifestyle status. However, given the strong confounding effect of socioeconomic status and health-promoting behaviours in relation to breastfeeding, future studies should explore this issue further to clarify whether breastfeeding per se is linked to long-term cardiovascular health.

In addition, the causal pathways and mechanisms underlying longitudinal associations require more exploration. For example, the mechanism linking breastfeeding and longer-term cardiovascular health is largely unknown and needs further examination. Mechanisms that can explain potential gender differences with respect to various cardiovascular risk factors/outcomes also require more research.

Future research efforts can help complete a more comprehensive picture of the role of innovative risk factors for CVD among the middle-aged and older adult population. Generating more gender-specific evidence is vital to better inform public health guidelines and policies with a gender focus. It is hoped that this innovative thesis will lay the groundwork for future explorations of innovative risk factors for CVD as well as gender differences, with the potential to influence public health policy and guidelines, and ultimately improve the health of middle-aged and older men and women.

8.5 REFERENCES

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APPENDICES

Appendix 1 - Additional gender analysis relating to Chapter 4

Summary of main findings

The findings from this additional gender analysis are presented in **Tables 1 to 6** in this appendix. The unadjusted and adjusted odds ratios (ORs) for incident type 2 diabetes mellitus (T2DM) by levels of body mass index, physical activity and sitting in women (n=16,156) and men (n=13,416) are reported in **Tables 1** and **2** respectively. In both women and men, compared with normal weight counterparts, being overweight or obese was significantly associated with higher odds of incident T2DM in unadjusted and adjusted models. Compared with women in the low physical activity tertile, women in the high physical activity tertile had significantly lower odds of developing T2DM in the unadjusted and adjusted models. Compared with men in the low physical activity tertile, men in the medium physical activity tertile had significantly lower odds of developing T2DM in the unadjusted model only. Women in the higher sitting category compared with those in the lower sitting category had significantly lower odds of incident T2DM in both unadjusted and adjusted models. ORs were not significantly different between categories of sitting in men.

Adjusted ORs for associations between physical activity or sitting time and incident T2DM, stratified by body mass index, in women and men are presented in **Tables 3** and **4** respectively. In both women and men, OR were not significantly different between body mass index categories for different levels of PA and sitting, and overall no significant interactions were found.

Adjusted ORs for associations between combinations of body mass index, physical activity and sitting and incident T2DM in women and men are included in **Tables 5** and **6** respectively. Overall, normal weight women and men with low physical activity and higher sitting levels had lower odds of developing T2DM than overweight or obese counterparts with high physical activity and lower sitting levels.

Findings from this additional gender analysis were generally similar to those presented in **Chapter 4**. Being overweight or obese was a relatively stronger risk factor than low physical activity or high sitting levels. The increased odds of developing T2DM associated with being overweight or obese were not offset by high physical activity or low sitting levels.

Table 1. **Unadjusted and adjusted odds ratios for incident type 2 diabetes in women (n=16,156) by levels of body mass index, physical activity and sitting (2006-10).**

	Unadjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios[a] (95% CI)	p-value
Body mass index category				
Normal weight (18.5 to <25 kg/m^2)	1.0 (reference)		1.0 (reference)	
Overweight (25 to <30 kg/m^2)	2.27 (1.66, 3.10)	<0.001	2.14 (1.56, 2.94)	<0.001
Obese (≥30 kg/m^2)	4.76 (3.49, 6.48)	<0.001	4.63 (3.36, 6.39)	<0.001
Physical activity[b] tertiles				
Low (0 to <300 min/week)	1.0 (reference)		1.0 (reference)	
Medium (300 to <660 min/week)	0.89 (0.67, 1.18)	0.42	1.03 (0.78, 1.37)	0.83
High (≥660 min/week)	0.68 (0.50, 0.91)	0.01	0.78 (0.57, 1.07)	0.12
Sitting time category				
Lower sitting (<8 hours/day)	1.0 (reference)		1.0 (reference)	
Higher sitting (≥8 hours/day)	0.55 (0.35, 0.87)	0.01	0.55 (0.35, 0.87)	0.01

Abbreviations: CI=confidence interval, kg=kilograms, m=meter, min=minutes.

Data for n=16,156 included in analysis, of which 276 developed diabetes.

[a] Adjusted for age group, follow-up time, country of birth, education, family history of diabetes and lifestyle risk factors (body mass index category/physical activity tertiles/sitting time category).

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week.

Table 2. **Unadjusted and adjusted odds ratios for incident type 2 diabetes in men (n=13,416) by levels of body mass index, physical activity and sitting (2006-10).**

	Unadjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios[a] (95% CI)	p-value
Body mass index category				
Normal weight (18.5 to <25 kg/m^2)	1.0 (reference)		1.0 (reference)	
Overweight (25 to <30 kg/m^2)	1.94 (1.42, 2.66)	<0.001	1.96 (1.43, 2.70)	<0.001
Obese (≥30 kg/m^2)	5.44 (3.94, 7.51)	<0.001	5.62 (4.03, 7.85)	<0.001
Physical activity[b] tertiles				
Low (0 to <300 min/week)	1.0 (reference)		1.0 (reference)	
Medium (300 to <660 min/week)	0.75 (0.58, 0.99)	0.04	0.86 (0.66, 1.13)	0.28
High (≥660 min/week)	0.79 (0.61, 1.02)	0.08	0.94 (0.72, 1.22)	0.62
Sitting time category				
Lower sitting (<8 hours/day)	1.0 (reference)		1.0 (reference)	
Higher sitting (≥8 hours/day)	1.07 (0.81, 1.41)	0.64	1.15 (0.87, 1.54)	0.33

Abbreviations: CI=confidence interval, kg=kilograms, m=meter, min=minutes.

Data for n=13,416 included in analysis, of which 335 developed diabetes.

[a] Adjusted for age group, follow-up time, country of birth, education, family history of diabetes and lifestyle risk factors (body mass index category/physical activity tertiles/sitting time category).

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week.

Table 3. Adjusted odds ratios for associations between physical activity/sitting and incident type 2 diabetes in women (n=16,156) stratified by body mass index (BMI) categories.

Variable	BMI category		
	Normal weight (18.5 to <25 kg/m^2) N=7,905	**Overweight (25 to <30 kg/m^2) N=5,447**	**Obese (≥30 kg/m^2) N=2,804**
	Adjusted Odds Ratios[a] (95% CI)	**Adjusted Odds Ratios[a] (95% CI)**	**Adjusted Odds Ratios[a] (95% CI)**
Physical activity[b] tertiles			
Low (0 to <300 min/week)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Medium (300 to <660 min/week)	1.42 (0.76, 2.65); p=0.28	0.94 (0.58, 1.53); p=0.82	0.97 (0.62, 1.51); p=0.89
High (≥660 min/week)	0.84 (0.43, 1.63); p=0.60	0.88 (0.53, 1.44); p=0.60	0.65 (0.38, 1.10); p=0.11
Sitting time category (%)			
Lower sitting (<8 hours/day)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Higher sitting (≥8 hours/day)	0.14 (0.02, 1.04); p=0.05	0.60 (0.29, 1.26); p=0.18	0.67 (0.36, 1.24); p=0.20

Abbreviations: BMI=body mass index, CI=confidence interval, kg=kilograms, m=meter, min=minutes, p=probability.

[a] Adjusted for age group, follow-up time, country of birth, education, family history of diabetes and sitting time/physical activity.

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week.

Table 4. Adjusted odds ratios for associations between physical activity/sitting and incident type 2 diabetes in men (n=13,416) stratified by body mass index (BMI) categories.

Variable	BMI category		
	Normal weight (18.5 to <25 kg/m^2) N=4,538	**Overweight (25 to <30 kg/m^2) N=6,691**	**Obese (≥30 kg/m^2) N=2,187**
	Adjusted Odds Ratios[a] (95% CI)	**Adjusted Odds Ratios[a] (95% CI)**	**Adjusted Odds Ratios[a] (95% CI)**
Physical activity[b] tertiles			
Low (0 to <300 min/week)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Medium (300 to <660 min/week)	1.06 (0.54, 2.10); p=0.86	0.82 (0.54, 1.24); p=0.34	0.86 (0.56, 1.34); p=0.52
High (≥660 min/week)	0.77 (0.38, 1.55); p=0.46	1.00 (0.68, 1.48); p=0.99	0.96 (0.62, 1.47); p=0.83
Sitting time category (%)			
Lower sitting (<8 hours/day)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Higher sitting (≥8 hours/day)	1.10 (0.52, 2.34); p=0.81	1.25 (0.82, 1.91); p=0.30	1.04 (0.66, 1.64); p=0.86

Abbreviations: BMI=body mass index, CI=confidence interval, kg=kilograms, m=meter, min=minutes, p=probability.

[a] Adjusted for age group, follow-up time, country of birth, education, family history of diabetes and sitting time/physical activity.

[b] Physical activity was calculated as the sum of time spent on walking, moderate-intensity physical activity, and vigorous-intensity physical activity (weighted by two) in the past week.

Table 5. **Adjusted odds ratios for incident type 2 diabetes in women (n=16,156) based on body mass index-physical activity (BMI-PA) and BMI-PA-sitting combinations.**

Variable	Adjusted Odds Ratios					
	Model 1[a]		Model 2[b]		Model 3[c]	
	Adjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios (95% CI)	p-value
BMI-PA combination group[d]						
Normal weight-high PA	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA	1.47 (0.84, 2.58)	0.18	1.45 (0.83, 2.55)	0.19	1.52 (0.86, 2.66)	0.15
Normal weight-low PA	1.06 (0.55, 2.02)	0.87	1.03 (0.54, 1.97)	0.93	1.00 (0.52, 1.93)	0.99
Overweight-high PA	2.50 (1.45, 4.30)	0.001	2.51 (1.46, 4.32)	0.001	2.38 (1.38, 4.11)	0.002
Overweight-med PA	2.57 (1.50, 4.41)	0.001	2.54 (1.48, 4.36)	0.001	2.50 (1.45, 4.30)	0.001
Overweight-low PA	2.81 (1.64, 4.80)	<0.001	2.74 (1.60, 4.70)	<0.001	2.66 (1.55, 4.57)	<0.001
Obese-high PA	4.03 (2.20, 7.38)	<0.001	4.05 (2.21, 7.41)	<0.001	3.92 (2.13, 7.19)	<0.001
Obese-med PA	6.38 (3.73, 10.92)	<0.001	6.31 (3.68, 10.81)	<0.001	5.88 (3.42, 10.11)	<0.001
Obese-low PA	6.76 (4.07, 11.22)	<0.001	6.61 (3.97, 11.01)	<0.001	6.16 (3.69, 10.30)	<0.001

BMI-PA-sitting combination group[d]						
Normal weight-high PA-lower sitting	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA-lower sitting	1.54 (0.88, 2.71)	0.13	1.52 (0.87, 2.67)	0.14	1.58 (0.90, 2.78)	0.11
Normal weight-low PA-lower sitting	1.07 (0.55, 2.08)	0.83	1.05 (0.54, 2.03)	0.89	1.01 (0.52, 1.97)	0.77
Normal weight-high PA-higher sitting	0.00 (0.00, -)	0.99	0.00 (0.00, -)	0.99	0.00 (0.00, -)	0.99
Normal weight-med PA-higher sitting	0.00 (0.00, -)	0.99	0.00 (0.00, -)	0.99	0.00 (0.00, -)	0.99
Normal weight-low PA-higher sitting	0.42 (0.06, 3.12)	0.40	0.41 (0.05, 3.05)	0.38	0.41 (0.06, 3.06)	0.38
Overweight-high PA-lower sitting	2.46 (1.42, 4.25)	0.001	2.47 (1.43, 4.27)	0.001	2.34 (1.35, 4.05)	0.002
Overweight-med PA-lower sitting	2.63 (1.52, 4.54)	0.001	2.60 (1.50, 4.49)	0.001	2.54 (1.47, 4.41)	0.001
Overweight-low PA-lower sitting	2.60 (1.49, 4.53)	0.001	2.54 (1.45, 4.43)	0.001	2.46 (1.41, 4.30)	0.002
Overweight-high PA-higher sitting	0.87 (0.12, 6.49)	0.89	0.87 (0.12, 6.51)	0.89	0.83 (0.11, 6.22)	0.85
Overweight-med PA-higher sitting	0.97 (0.23, 4.14)	0.96	0.96 (0.22, 4.11)	0.96	0.96 (0.22, 4.11)	0.95
Overweight-low PA-higher sitting	2.65 (0.99, 7.07)	0.05	2.60 (0.97, 6.95)	0.06	2.54 (0.95, 6.79)	0.06
Obese-high PA-lower sitting	3.92 (2.12, 7.24)	<0.001	3.94 (2.13, 7.28)	<0.001	3.81 (2.06, 7.06)	<0.001
Obese-med PA-lower sitting	6.19 (3.57, 10.73)	<0.001	6.12 (3.53, 10.62)	<0.001	5.66 (3.25, 9.87)	<0.001
Obese-low PA-lower sitting	6.65 (3.95, 11.17)	<0.001	6.51 (3.86, 10.97)	<0.001	6.00 (3.54, 10.15)	<0.001
Obese-high PA-higher sitting	1.98 (0.26, 14.90)	0.51	1.98 (0.26, 14.90)	0.51	1.90 (0.25, 14.38)	0.53
Obese-med PA-higher sitting	4.34 (1.47, 12.81)	0.008	4.30 (1.46, 12.71)	0.008	4.15 (1.40, 12.32)	0.01

Obese-low PA-higher sitting	4.55 (1.92, 10.81)	0.001	4.46 (1.88, 10.61)	0.001	4.35 (1.82, 10.41)	0.001

Abbreviations: BMI=body mass index, CI=confidence interval, med=medium, p=probability, PA=physical activity.

[a] Adjusted for age group only.

[b] Adjusted for age group, follow-up time and BMI-PA/BMI-PA-sitting combination groups.

[c] Adjusted for age group, follow-up time, country of birth, highest education, family history of diabetes and BMI-PA/BMI-PA-sitting combination groups.

[d] BMI categories defined as: normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (≥30 kg/m^2). PA categories based on PA tertiles: high (≥660 min/week), medium (300-<660 min/week) and low (0 to <300 min/week). Based on previous analysis, sitting was dichotomised as higher (≥8 hours/day) and lower (<8 hours/day) sitting.

Table 6. Adjusted odds ratios for incident type 2 diabetes in men (n=13,416) based on body mass index-physical activity (BMI-PA) and BMI-PA-sitting combinations.

Variable	Adjusted Odds Ratios					
	Model 1[a]		Model 2[b]		Model 3[c]	
	Adjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios (95% CI)	p-value	Adjusted Odds Ratios (95% CI)	p-value
BMI-PA combination group[d]						
Normal weight-high PA	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA	1.30 (0.68, 2.51)	0.43	1.22 (0.63, 2.35)	0.56	1.23 (0.64, 2.38)	0.54
Normal weight-low PA	1.34 (0.69, 2.62)	0.39	1.22 (0.63, 2.39)	0.56	1.19 (0.61, 2.33)	0.61
Overweight-high PA	2.33 (1.36, 3.99)	0.002	2.34 (1.37, 4.01)	0.002	2.31 (1.35, 3.96)	0.002
Overweight-med PA	2.04 (1.16, 3.56)	0.01	1.93 (1.10, 3.38)	0.02	1.95 (1.11, 3.41)	0.02
Overweight-low PA	2.65 (1.55, 4.53)	<0.001	2.42 (1.41, 4.15)	0.001	2.40 (1.40, 4.11)	0.002
Obese-high PA	6.43 (3.65, 11.35)	<0.001	6.58 (3.73, 11.63)	<0.001	6.34 (3.58, 11.23)	<0.001
Obese-med PA	5.97 (3.35, 10.65)	<0.001	5.92 (3.32, 10.55)	<0.001	5.85 (3.27, 10.45)	<0.001
Obese-low PA	7.64 (4.46, 13.09)	<0.001	7.16 (4.18, 12.28)	<0.001	6.95 (4.04, 11.95)	<0.001

BMI-PA-sitting combination group[d]						
Normal weight-high PA-lower sitting	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Normal weight-med PA-lower sitting	1.12 (0.54, 2.32)	0.76	1.03 (0.50, 2.14)	0.93	1.04 (0.50, 2.16)	0.91
Normal weight-low PA-lower sitting	1.34 (0.65, 2.72)	0.43	1.20 (0.59, 2.45)	0.62	1.18 (0.58, 2.42)	0.65
Normal weight-high PA-higher sitting	0.51 (0.07, 3.90)	0.52	0.52 (0.07, 3.90)	0.52	0.53 (0.07, 4.03)	0.54
Normal weight-med PA-higher sitting	1.70 (0.62, 4.64)	0.31	1.65 (0.60, 4.53)	0.33	1.72 (0.63, 4.74)	0.29
Normal weight-low PA-higher sitting	1.06 (0.31, 3.66)	0.92	1.01 (0.29, 3.47)	0.99	0.96 (0.28, 3.34)	0.95
Overweight-high PA-lower sitting	2.26 (1.29, 3.94)	0.004	2.27 (1.30, 3.96)	0.004	2.24 (1.28, 3.92)	0.005
Overweight-med PA-lower sitting	2.02 (1.12, 3.62)	0.02	1.91 (1.06, 3.42)	0.03	1.93 (1.07, 3.47)	0.03
Overweight-low PA-lower sitting	2.16 (1.21, 3.85)	0.009	1.95 (1.09, 3.49)	0.02	1.92 (1.07, 3.44)	0.03
Overweight-high PA-higher sitting	1.88 (0.69, 5.15)	0.22	1.88 (0.69, 5.16)	0.22	1.85 (0.67, 5.08)	0.23
Overweight-med PA-higher sitting	1.58 (0.62, 4.04)	0.34	1.52 (0.59, 3.89)	0.39	1.53 (0.60, 3.92)	0.38
Overweight-low PA-higher sitting	3.85 (1.96, 7.57)	<0.001	3.63 (1.85, 7.13)	<0.001	3.71 (1.88, 7.30)	<0.001
Obese-high PA-lower sitting	6.04 (3.34, 10.92)	<0.001	6.21 (3.43, 11.24)	<0.001	6.00 (3.30, 10.89)	<0.001
Obese-med PA-lower sitting	5.47 (2.93, 10.18)	<0.001	5.42 (2.91, 10.10)	<0.001	5.32 (2.85, 9.94)	<0.001
Obese-low PA-lower sitting	7.40 (4.19, 13.07)	<0.001	6.79 (3.84, 12.02)	<0.001	6.53 (3.68, 11.59)	<0.001
Obese-high PA-higher sitting	6.75 (2.42, 18.83)	<0.001	6.67 (2.38, 18.64)	0.001	6.33 (2.25, 17.79)	0.001
Obese-med PA-higher sitting	6.43 (2.81, 14.75)	<0.001	6.36 (2.77, 14.60)	<0.001	6.46 (2.81, 14.87)	<0.001

Obese-low PA-higher sitting	6.87 (3.27, 14.43)	<0.001	6.89 (3.28, 14.48)	<0.001	6.91 (3.28, 14.57)	<0.001

Abbreviations: BMI=body mass index, CI=confidence interval, med=medium, p=probability, PA=physical activity.

[a] Adjusted for age group only.

[b] Adjusted for age group, follow-up time and BMI-PA/BMI-PA-sitting combination groups.

[c] Adjusted for age group, follow-up time, country of birth, highest education, family history of diabetes and BMI-PA/BMI-PA-sitting combination groups.

[d] BMI categories defined as: normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (≥30 kg/m^2). PA categories based on PA tertiles: high (≥660 min/week), medium (300-<660 min/week) and low (0 to <300 min/week). Based on previous analysis, sitting was dichotomised as higher (≥8 hours/day) and lower (<8 hours/day) sitting.

Appendix 2 – Gender-specific 45 and Up Study baseline questionnaire and consent form

THE 45 AND UP STUDY

Research to improve health and wellbeing

45 and Up Study Questionnaire for Women

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences, to provide knowledge that will help people live healthy and fulfilling lives for as long as possible. Participation is completely voluntary, and you are free to withdraw from the Study at any time. To take part, please read the participant information leaflet, then complete the questionnaire and consent form and return them in the envelope provided. We very much hope you will be able to take part.

Any questions or comments? Please call the Study helpline: **1300 45 11 45** or go to **www.45andUp.org.au**

Auspiced by: the saxinstitute – Research Partnerships for Better Health

In collaboration with: The Cancer Council New South Wales; Heart Foundation; NSW Health; beyondblue; New South Wales Government; DADHC Department of Ageing, Disability & Home Care

Your answers and experiences are important to us.
To help us read your answers, please write as clearly as possible using a **BLACK** or **BLUE** pen, and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) [X] Yes [ ] No
OR put numbers in the appropriate box, e.g. *21st June 1945*
2 1 / 0 6 / 1 9 4 5 age 6 2

General questions about you

1. **What is your date of birth?** day / month / year: [ ][ ] / [ ][ ] / 1 9 [ ][ ]

2. **What is today's date?** day / month / year: [ ][ ] / [ ][ ] / 2 0 [ ][ ]

3. **How tall are you without shoes?** (please give to the nearest cm or inch)
[ ] cm **OR** [ ] feet [ ] inches

4. **About how much do you weigh?**
[ ] kg **OR** [ ] stone [ ] lbs

5. **What is the highest qualification you have completed?**
(please put a cross in the most appropriate box)
- [ ] no school certificate or other qualifications
- [ ] school or intermediate certificate (or equivalent)
- [ ] higher school or leaving certificate (or equivalent)
- [ ] trade/apprenticeship (e.g. hairdresser, chef)
- [ ] certificate/diploma (e.g. child care, technician)
- [ ] university degree or higher

6. **Are you of Aboriginal or Torres Strait Islander origin?**
(you can cross more than one box)
[ ] No [ ] Yes, Aboriginal [ ] Yes, Torres Strait Islander

7. **In which country were you born?**
[ ] Australia ▶ please go to question 9

[ ] UK	[ ] Ireland	[ ] Italy	[ ] China
[ ] Greece	[ ] New Zealand	[ ] Germany	[ ] Lebanon
[ ] Philippines	[ ] Netherlands	[ ] Vietnam	[ ] Malta
[ ] Poland	[ ] other *(please specify)* _____		

8. **What year did you first come to live in Australia for one year or more?** (e.g. 1970) [ ][ ][ ][ ]

9. **What is your ancestry?** (please cross up to 2 boxes)

[ ] Australian	[ ] English	[ ] Irish	[ ] Chinese
[ ] Italian	[ ] Greek	[ ] Scottish	[ ] German
[ ] Lebanese	[ ] Dutch	[ ] Maltese	[ ] Polish
[ ] Filipino	[ ] Indian	[ ] Croatian	[ ] Vietnamese

[ ] other *(please specify)* _____

10. **Do you speak a language other than English at home?**
[ ] Yes [ ] No

11. **Have you ever been a regular smoker?**
[ ] Yes ▼ [ ] No ▶ *If No – please go to question 12*

How old were you when you started smoking regularly? [ ][ ] years old

Are you a regular smoker now? [ ] Yes [ ] No

If No **– how old were you when you stopped smoking regularly?** [ ][ ] years old

About how much do you/did you smoke on average each day?
(If you are an ex-smoker, how much did you smoke on average when you smoked?)
[ ][ ] cigarettes per day [ ][ ] pipes and cigars per day

12. **About how many alcoholic drinks do you have each week?**
one drink = a glass of wine, middy of beer or nip of spirits
(put "0" if you do not drink, or have less than one drink each week)
[ ][ ] number of alcoholic drinks each week

13. **On how many days each week do you usually drink alcohol?** [ ] days each week

BLFF0710

14. What best describes your current situation? (please cross one box)

☐ single ☐ married ☐ de facto/living with a partner
☐ widowed ☐ divorced ☐ separated

15. What best describes your current housing? (please cross one box)

☐ house ☐ flat, unit, apartment ☐ house on farm
☐ hostel for the aged ☐ mobile home ☐ other
☐ nursing home ☐ retirement village, self care unit

16. How many TIMES did you do each of these activities LAST WEEK?
(put "0" if you did not do this activity)

	times in the last week
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐

17. If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?
(put "0" if you did not do this activity)

	hours	minutes
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐ :	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐ :	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐ :	☐☐

Questions about your family

18. Have your mother, father, brother(s) or sister(s) ever had:
(blood relatives only: please put a cross in the appropriate box(es))

	mother	father	brother/ sister		mother	father	brother/ sister
heart disease	☐	☐	☐	breast cancer	☐	☐	☐
high blood pressure	☐	☐	☐	bowel cancer	☐	☐	☐
stroke	☐	☐	☐	lung cancer	☐	☐	☐
diabetes	☐	☐	☐	melanoma	☐	☐	☐
dementia/Alzheimer's	☐	☐	☐	prostate cancer		☐	☐
Parkinson's disease	☐	☐	☐	ovarian cancer	☐		☐
severe depression	☐	☐	☐	osteoporosis	☐	☐	☐
severe arthritis	☐	☐	☐	hip fracture	☐	☐	☐
do not know	☐	☐	☐				

19. How many children have you given birth to? ☐☐ children
(please include stillbirths but do not include miscarriages, please write "0" if you have not had any children)

How old were you when you gave birth to your FIRST child? ☐☐ years old

How old were you when you gave birth to your LAST child? ☐☐ years old

For how many months, in total, have you breastfed? ☐☐ months
(please add together all the time you spent breastfeeding all of your children; put "0" if you never breastfed)

Questions about your health

20. About how many hours a week are you exposed to someone else's tobacco smoke?

hours per week ☐☐ at home
hours per week ☐☐ in other places *(e.g. work, going out, cars)*

21. Have you ever used the pill or other hormonal contraceptives?
(e.g. the combined pill, mini pill, contraceptive implant or injections)

☐ Yes ▼ ☐ No

If Yes, for how long altogether have you used hormonal contraceptives? ☐☐ years
(please write '0' if you used them for less than a year in total)

If Yes, how old were you when you LAST used hormonal contraceptives? ☐☐ age
(please write your current age if you are still using them)

Which type of pill or other hormonal contraceptive did you use MOST RECENTLY?

☐ "the pill", combined pill *(e.g. Microgynon, Levlen)*
☐ progesterone-only pill ("mini pill") *(e.g. Micronor, Noriday, Microval)*
☐ Depo Provera
☐ contraceptive implant *(e.g. Implanon, Norplant)*
☐ do not know

22. Have you ever used hormone replacement therapy (HRT)?

☐ Yes ▼ ☐ No

If Yes, for how long altogether have you used HRT? ☐☐ years
(please write '0' if you used HRT for less than a year in total)

Are you currently taking HRT? ☐ Yes ☐ No

If No, at what age did you stop? ☐☐ age

23. Have you taken any medications, vitamins or supplements for most of the last 4 weeks, including HRT and the pill?

☐ Yes ▼ ☐ No

If Yes, was it:		
☐ multivitamins + minerals	☐ multivitamins alone	☐ fish oil
☐ glucosamine	☐ omega 3	☐ paracetamol
☐ aspirin for the heart	☐ aspirin for other reasons	☐ Lipitor
☐ Avapro, Karvea	☐ warfarin, Coumadin	☐ Pravachol
☐ Coversyl, Coversyl Plus	☐ Lasix, frusemide	☐ Zocor, Lipex
☐ Cardizem, Vasocordol	☐ Micardis	☐ Nexium
☐ Norvasc	☐ Fosamax	☐ Somac
☐ Tritace	☐ Caltrate	☐ Losec, Acimax *omeprazole*
☐ Noten, Tenormin *atenolol*	☐ Oroxine *thyroxine*	☐ Ventolin *salbutamol*
☐ Zyloprim, Progout 300 *allopurinol*	☐ Diabex, Diaformin *metformin*	☐ Zoloft *sertraline*
☐ Cipramil *citaloprim*	☐ Efexor *venlafaxine*	

please list any other regular medications or supplements here

24. Has a doctor EVER told you that you have:
(If YES, please cross the box and give your age when the condition was first found)

	Yes	Age when condition was first found
skin cancer (not melanoma)	☐	☐☐ age
melanoma	☐	☐☐ age
breast cancer	☐	☐☐ age
other cancer	☐	☐☐ age
type of cancer *(please describe)*		
heart disease	☐	☐☐ age
type of heart disease *(please describe)*		
high blood pressure – when pregnant	☐	☐☐ age
high blood pressure – when not pregnant	☐	☐☐ age
stroke	☐	☐☐ age
diabetes	☐	☐☐ age
blood clot (thrombosis)	☐	☐☐ age
asthma	☐	☐☐ age
hayfever	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
Parkinson's disease	☐	☐☐ age
none of these	☐	

25. In the last month have you been treated for:
(If YES, please cross the box and give your age when the treatment started)

	Yes	Age started treatment
cancer	☐	☐☐ age
heart attack or angina	☐	☐☐ age
other heart disease	☐	☐☐ age
high blood pressure	☐	☐☐ age
high blood cholesterol	☐	☐☐ age
blood clotting problems	☐	☐☐ age
asthma	☐	☐☐ age
osteoarthritis	☐	☐☐ age
thyroid problems	☐	☐☐ age
osteoporosis or low bone density	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
none of these	☐	

26. Are you NOW suffering from any other important illness?
☐ Yes ▼ ☐ No

Please describe this illness and its treatment

27. Do you regularly need help with daily tasks because of long-term illness or disability?
(e.g. personal care, getting around, preparing meals)
☐ Yes ☐ No

28. Does your health now LIMIT YOU in any of the following activities?

	yes, limited a lot	**yes**, limited a little	**no**, not limited at all
VIGOROUS activities *(e.g. running, strenuous sports)*	☐	☐	☐
MODERATE activities *(e.g. pushing a vacuum cleaner, playing golf)*	☐	☐	☐
lifting or carrying shopping	☐	☐	☐
climbing several flights of stairs	☐	☐	☐
climbing one flight of stairs	☐	☐	☐
walking one kilometre	☐	☐	☐
walking half a kilometre	☐	☐	☐
walking 100 metres	☐	☐	☐
bending, kneeling or stooping	☐	☐	☐
bathing or dressing yourself	☐	☐	☐

29. Have you ever had any of the following operations?
(If YES, please cross the box and give your age when you had the operation; give your age at the **most recent operation** if you have had more than one)

	Yes	Age when had operation
removal of skin cancer	☐	☐☐ age
hysterectomy	☐	☐☐ age
both ovaries removed	☐	☐☐ age
sterilisation (tubes tied)	☐	☐☐ age
repair of prolapsed womb, bladder or bowel	☐	☐☐ age
knee replacement	☐	☐☐ age
hip replacement	☐	☐☐ age
gallbladder removed	☐	☐☐ age
heart or coronary bypass surgery *(include stents and balloons)*	☐	☐☐ age

other *(please describe any other operations you have had in the last 10 years, with your age when you had them)*

30. Do you regularly care for a sick or disabled family member or friend?

☐ Yes ▼ ☐ No

If Yes, about how much time each week do you usually spend caring for this person?

☐ full time OR ☐☐ hours/wk

31. In general, how would you rate your:

	excellent	very good	good	fair	poor
overall health?	☐	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐	☐
eyesight? *(with glasses or contact lenses, if you wear them)*	☐	☐	☐	☐	☐
memory?	☐	☐	☐	☐	☐
teeth and gums?	☐	☐	☐	☐	☐

32. Do you feel you have a hearing loss? ☐ Yes ☐ No

33. How many of your own teeth do you have left?

☐ None – all of my teeth are missing ☐ 1-9 teeth left
☐ 10-19 teeth left ☐ 20 or more teeth left

34. During the past 12 months, how many times have you fallen to the floor or ground? (put "0" if you haven't fallen in this time)

☐☐ times

35. Have you had a broken/fractured bone in the last 5 years?

☐ Yes ▼ ☐ No

If Yes, which bones were broken?

☐ wrist ☐ arm ☐ hip ☐ ankle
☐ rib ☐ finger/toe ☐ other _____

How old were you when it happened? (give age at most recent fracture if more than one) ☐☐ years old

36. About how many times a week are you usually troubled by leaking urine?

☐ never ☐ once a week or less
☐ 2-3 times ☐ 4-6 times ☐ every day

37. Have you been through menopause?

☐ No
☐ Not sure *(because hysterectomy, taking HRT, etc.)*
☐ My periods have become irregular
☐ Yes – How old were you when you went through menopause? ☐☐ years old

38. Have you ever been for a breast screening mammogram?

☐ Yes ▼ ☐ No

If Yes, what year did you have your last mammogram? (e.g. 2005) ☐☐☐☐

How many times have you been for breast screening altogether? ☐☐ times

39. Have you ever been screened for colorectal (bowel) cancer?

☐ Yes ▼ ☐ No

If Yes, please indicate which test(s) you had:

☐ faecal occult blood test *(test for blood in the stool/faeces)*
☐ sigmoidoscopy *(a tube is used to examine the lower bowel: this is usually done in a doctor's office without pain relief)*
☐ colonoscopy *(a long tube is used to examine the whole large bowel; you would usually have to have an enema or drink large amounts of special liquid to prepare the bowel for this)*

What year did you have the most recent one of these tests? (e.g. 2005) ☐☐☐☐

Questions about your diet

40. About how many times each week do you eat: (please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

	number of times eaten each week
beef, lamb or pork	☐☐
chicken, turkey or duck	☐☐
processed meat *(include bacon, sausages, salami, devon, burgers, etc)*	☐☐
fish or seafood	☐☐
cheese	☐☐

41. About how many of the following do you usually eat:

slices or pieces of brown/wholemeal bread each week *(also include multigrain, rye bread, etc.)* ☐☐

bowls of breakfast cereal each week ☐☐

If you eat breakfast cereal is it usually: (please cross)

☐ bran cereal *(allbran, branflakes, etc.)* ☐ muesli
☐ biscuit cereal *(weetbix, shredded wheat, etc.)* ☐ other *(cornflakes, rice bubbles,etc.)*
☐ oat cereal *(porridge, etc.)*

42. Which type of milk do you mostly have?

☐ whole milk ☐ reduced fat milk ☐ skim milk
☐ soy milk ☐ other milk ☐ I don't drink milk

43. About how many serves of vegetables do you usually eat each day? A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)

☐☐ number of serves of cooked vegetables each day
☐☐ number of serves of raw vegetables each day (e.g. salad)
☐ I don't eat vegetables

44. About how many serves of fruit or glasses of fruit juice do you usually have each day? A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)

☐☐ number of serves of fruit each day
☐☐ number of glasses of fruit juice each day
☐ I don't eat fruit

45. Please put a cross in the box if you NEVER eat:

☐ red meat ☐ chicken/poultry ☐ pork/ham ☐ dairy products
☐ any meat ☐ eggs ☐ sugar ☐ wheat products
☐ fish ☐ seafood ☐ cream ☐ cheese

Questions about time and work

46. What is your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation, etc)

☐ less than $5,000 per year ☐ $30,000-$39,999 per year
☐ $5,000-$9,999 per year ☐ $40,000-$49,999 per year
☐ $10,000-$19,999 per year ☐ $50,000-$69,999 per year
☐ $20,000-$29,999 per year ☐ $70,000 or more per year
☐ I would rather not answer this question

47. What is your current work status? (you can cross more than one box)

- ☐ in full time paid work
- ☐ in part time paid work
- ☐ completely retired/pensioner
- ☐ partially retired
- ☐ disabled/sick
- ☐ other
- ☐ self-employed
- ☐ doing unpaid work
- ☐ studying
- ☐ looking after home/family
- ☐ unemployed

48. If you are partially or completely retired, how old were you when you retired? ☐☐ years old

Why did you retire? (you can cross more than one box)

- ☐ reached usual retirement age
- ☐ to care for family member/friend
- ☐ made redundant
- ☐ other
- ☐ lifestyle reasons
- ☐ ill health
- ☐ could not find a job

49. About how many HOURS each WEEK do you usually spend doing the following? (please put "0" if you do not spend any time doing it)

hours per week ☐☐ paid work

hours per week ☐☐ voluntary/unpaid work

50. Which of the following do you have? (excluding Medicare)

- ☐ Private health insurance – with extras
- ☐ Private health insurance – without extras
- ☐ Department of Veterans' Affairs white or gold card
- ☐ Health care concession card
- ☐ none of these

51. What best describes the colour of the skin on the inside of your upper arm, that is your skin colour without any tanning?

- ☐ very fair
- ☐ fair
- ☐ light olive
- ☐ dark olive
- ☐ brown
- ☐ black

52. What would happen if your skin was repeatedly exposed to bright sunlight during summer without any protection? Would it:

- ☐ Get very tanned?
- ☐ Get moderately tanned?
- ☐ Get mildly or occasionally tanned?
- ☐ Never tan, or only get freckled?

53. About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?

hours per day ☐☐ weekday

hours per day ☐☐ weekend

54. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it)

hours per day		hours per day	
☐☐	sleeping (including at night & naps)	☐☐	sitting
☐☐	watching television or using a computer	☐☐	standing

55. How many TIMES in the LAST WEEK did you:
(please put "0" if you did not spend any time doing it)

	times in the last week
spend time with friends or family who do not live with you?	☐☐
talk to someone (friends, relatives or others) on the telephone?	☐☐
go to meetings of social clubs, religious groups or other groups you belong to?	☐☐

56. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to? ☐☐ people

57. During the past 4 weeks, about how often did you feel:

	none of the time	a little of the time	some of the time	most of the time	all of the time
tired out for no good reason?	☐	☐	☐	☐	☐
nervous?	☐	☐	☐	☐	☐
so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
hopeless?	☐	☐	☐	☐	☐
restless or fidgety?	☐	☐	☐	☐	☐
so restless that you could not sit still?	☐	☐	☐	☐	☐
depressed?	☐	☐	☐	☐	☐
that everything was an effort?	☐	☐	☐	☐	☐
so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
worthless?	☐	☐	☐	☐	☐

58. During the past 4 weeks, have you had any of the following problems with your work or daily activities because of any emotional problems (such as being depressed or anxious)?

cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
achieved less than you would have liked to	☐ Yes	☐ No
did work or other activities less carefully than usual	☐ Yes	☐ No

Thank you very much for filling in the questionnaire

DON'T FORGET TO SIGN THE CONSENT FORM OVERLEAF

Are your name and address correct on the front of this questionnaire? ☐ Yes ☐ No

If INCORRECT, give details below.

Surname:

Given name(s):

Postal address:

Town or Suburb:

State or Territory: Postcode:

Consent form

THE 45 AND UP STUDY
Research to improve health and wellbeing

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences and to have their health followed over time. By signing this form you are agreeing to take part in the *45 and Up Study* and for the Study team to follow your health over time. Participation is completely voluntary, and you are free to ask questions or to withdraw from the Study at any time, by calling the Study helpline on 1300 45 11 45. More information on the Study can be found at www.45andup.org.au

I agree to have my health followed over time through:

the 45 and Up Study team following health and other records relating to me, including NSW hospital records, cancer records, death records and other health-related records, as outlined in the Study leaflet: *The 45 and Up Study: Information for participants*;

Medicare Australia releasing to the 45 and Up Study my enrolment details, including Medicare number, and information concerning services provided to me under Medicare, the Department of Veterans' Affairs, the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme, including past information, until the end of the Study or for the duration of my involvement in the Study;

being contacted in the future to provide information on changes to my health and lifestyle. I may also be asked to provide further information including questionnaire responses or biological samples; my participation in any of these would be completely voluntary.

I give my consent on the understanding that:

my information will only be used for the purposes outlined in the Study leaflet entitled *The 45 and Up Study: Information for participants*, of which I have a copy;

my information will be kept strictly confidential and will be used for health research only;

reports and publications from the Study will be based on de-identified information and will not identify any individual taking part;

my participation in this Study is entirely voluntary and my consent will continue to be valid following death or disablement unless withdrawn by my next of kin or other person responsible. I am free to withdraw from the Study at any time by calling the **Study helpline on 1300 45 11 45;**

my decision on whether or not to take part in the Study or in any additional research will not disadvantage me or affect my future health care in any way.

I have been provided with information about the 45 and Up Study including how it will gather, store, use and disclose information about me, in the Study leaflet. I have been given an opportunity to ask questions and have been fully informed about the Study.

Name (Print): _____

Signature: _____ Date today: day ☐☐ / month ☐☐ / year 2 0 ☐☐

Extra contact details

It would be very helpful and reduce Study costs if we could contact you in future by email. If you are happy for us to do this, please write your email address here:

Email address: _____

Sometimes we find that people have moved when we try to contact them again. It would be very helpful if you could give us your mobile phone number and/or the contact details of someone close to you (such as a relative or friend) who would be happy for us to contact them if we are unable to reach you. We would only get in touch with that person if we were unable to contact you directly and we would need to tell them our reason for contacting you. Please leave this section blank if you do not wish to provide these extra contact details.

Your home phone number: (☐☐) _____ Your mobile phone number: _____

Full name of contact person: _____

Phone number of contact person: (☐☐) _____

If you have any questions about the Study, please ring the Study helpline on **1300 45 11 45**.
You can also write to or send your questionnaire (no stamp required) directly to:

Associate Professor Emily Banks, Scientific Director,
The 45 and Up Study, Reply paid 5289, Sydney NSW 2001.

Thank you very much for taking part

THE 45 AND UP STUDY

Research to improve health and wellbeing

45 and Up Study Questionnaire for Men

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences, to provide knowledge that will help people live healthy and fulfilling lives for as long as possible. Participation is completely voluntary, and you are free to withdraw from the Study at any time. To take part, please read the participant information leaflet, then complete the questionnaire and consent form and return them in the envelope provided. We very much hope you will be able to take part.

Any questions or comments? Please call the Study helpline: **1300 45 11 45** or go to **www.45andUp.org.au**

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The Cancer Council New South Wales

Heart Foundation

NSW HEALTH

beyondblue the national depression initiative

New South Wales Government

DADHC Department of Ageing, Disability & Home Care

Your answers and experiences are important to us.
To help us read your answers, please write as clearly as possible using a **BLACK** or **BLUE** pen, and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) [X] Yes [ ] No
OR put numbers in the appropriate box, e.g. *21st June 1945*
2 1 / 0 6 / 1 9 4 5 age 6 2

General questions about you

1. **What is your date of birth?** day / month / year 1 9
2. **What is today's date?** day / month / year 2 0
3. **How tall are you without shoes?** (please give to the nearest cm or inch) ____ cm **OR** ____ feet ____ inches
4. **About how much do you weigh?** ____ kg **OR** ____ stone ____ lbs
5. **What is the highest qualification you have completed?** (please put a cross in the most appropriate box)
   - [ ] no school certificate or other qualifications
   - [ ] school or intermediate certificate (or equivalent)
   - [ ] higher school or leaving certificate (or equivalent)
   - [ ] trade/apprenticeship (e.g. hairdresser, chef)
   - [ ] certificate/diploma (e.g. child care, technician)
   - [ ] university degree or higher
6. **Are you of Aboriginal or Torres Strait Islander origin?** (you can cross more than one box)
   - [ ] No [ ] Yes, Aboriginal [ ] Yes, Torres Strait Islander
7. **In which country were you born?**
   - [ ] Australia ▶ please go to question 9
   - [ ] UK [ ] Ireland [ ] Italy [ ] China
   - [ ] Greece [ ] New Zealand [ ] Germany [ ] Lebanon
   - [ ] Philippines [ ] Netherlands [ ] Vietnam [ ] Malta
   - [ ] Poland [ ] other *(please specify)*_____
8. **What year did you first come to live in Australia for one year or more?** (e.g. 1970) ____
9. **What is your ancestry?** (please cross up to 2 boxes)
   - [ ] Australian [ ] English [ ] Irish [ ] Chinese
   - [ ] Italian [ ] Greek [ ] Scottish [ ] German
   - [ ] Lebanese [ ] Dutch [ ] Maltese [ ] Polish
   - [ ] Filipino [ ] Indian [ ] Croatian [ ] Vietnamese
   - [ ] other *(please specify)* _____
10. **Do you speak a language other than English at home?**
    - [ ] Yes [ ] No
11. **Have you ever been a regular smoker?**
    - [ ] Yes ▼ [ ] No ▶ *If No – please go to question 12*

    How old were you when you started smoking regularly? ____ years old
    Are you a regular smoker now? [ ] Yes [ ] No
    If No – how old were you when you stopped smoking regularly? ____ years old
    About how much do you/did you smoke on average each day?
    (If you are an ex-smoker, how much did you smoke on average when you smoked?)
    ____ cigarettes per day ____ pipes and cigars per day
12. **About how many alcoholic drinks do you have each week?**
    one drink = a glass of wine, middy of beer or nip of spirits
    (put "0" if you do not drink, or have less than one drink each week)
    ____ number of alcoholic drinks each week
13. **On how many days each week do you usually drink alcohol?** ____ days each week

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14. What best describes your current situation? (please cross one box)

☐ single ☐ married ☐ de facto/living with a partner
☐ widowed ☐ divorced ☐ separated

15. What best describes your current housing? (please cross one box)

☐ house ☐ flat, unit, apartment ☐ house on farm
☐ hostel for the aged ☐ mobile home ☐ other
☐ nursing home ☐ retirement village, self care unit

16. How many TIMES did you do each of these activities LAST WEEK?
(put "0" if you did not do this activity)

	times in the last week
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐

17. If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?
(put "0" if you did not do this activity)

	hours	minutes
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	☐☐ :	☐☐
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	☐☐ :	☐☐
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	☐☐ :	☐☐

Questions about your family

18. Have your mother, father, brother(s) or sister(s) ever had:
(blood relatives only: please put a cross in the appropriate box(es))

	mother	father	brother/ sister		mother	father	brother/ sister
heart disease	☐	☐	☐	breast cancer	☐	☐	☐
high blood pressure	☐	☐	☐	bowel cancer	☐	☐	☐
stroke	☐	☐	☐	lung cancer	☐	☐	☐
diabetes	☐	☐	☐	melanoma	☐	☐	☐
dementia/Alzheimer's	☐	☐	☐	prostate cancer		☐	☐
Parkinson's disease	☐	☐	☐	ovarian cancer	☐		☐
severe depression	☐	☐	☐	osteoporosis	☐	☐	☐
severe arthritis	☐	☐	☐	hip fracture	☐	☐	☐
do not know	☐	☐	☐				

19. How many children have you fathered? ☐☐ children
(please include stillbirths but do not include miscarriages, please write "0" if you have not had any children)

How old were you when you fathered your FIRST child? ☐☐ years old

How old were you when you fathered your LAST child? ☐☐ years old

20. Have you ever tried for more than 1 year but have been unable to father children?

☐ Yes ☐ No

Questions about your health

21. About how many hours a week are you exposed to someone else's tobacco smoke?

hours per week ☐☐ at home
hours per week ☐☐ in other places *(e.g. work, going out, cars)*

22. Over the last month, how often have you:

	not at all	some times	often	almost always
found it difficult to postpone urination?	☐	☐	☐	☐
had to push or strain to start urination?	☐	☐	☐	☐
had a weak urinary stream?	☐	☐	☐	☐
stopped and started again several times when you urinated?	☐	☐	☐	☐
had to urinate again less than 2 hours after you finished urinating?	☐	☐	☐	☐
had the feeling that you had not emptied your bladder completely after urinating?	☐	☐	☐	☐

Over the past month, how many times did you usually get up from bed to urinate during the night?

☐ never ☐ some nights ☐☐ times each night

23. Have you taken any medications, vitamins or supplements for most of the last 4 weeks?

☐ Yes ▼ ☐ No

If Yes, was it:

☐ multivitamins + minerals	☐ multivitamins alone	
☐ fish oil	☐ glucosamine	☐ omega 3
☐ paracetamol	☐ aspirin for the heart	☐ aspirin for other reasons
☐ Lipitor	☐ Avapro, Karvea	☐ warfarin, Coumadin
☐ Pravachol	☐ Coversyl, Coversyl Plus	☐ Lasix, frusemide
☐ Zocor, Lipex	☐ Cardizem, Vasocordol	☐ Micardis
☐ Nexium	☐ Norvasc	☐ Fosamax
☐ Somac	☐ Tritace	☐ Caltrate
☐ Losec, Acimax *omeprazole*	☐ Noten, Tenormin *atenolol*	☐ Oroxine *thyroxine*
☐ Ventolin *salbutamol*	☐ Zyloprim, Progout 300 *allopurinol*	☐ Diabex, Diaformin *metformin*
☐ Zoloft *sertraline*	☐ Cipramil *citaloprim*	☐ Efexor *venlafaxine*

please list any other regular medications or supplements here

24. Has a doctor EVER told you that you have:
(If YES, please cross the box and give your age when the condition was first found)

	Yes	Age when condition was first found
skin cancer (not melanoma)	☐	☐☐ age
melanoma	☐	☐☐ age
prostate cancer	☐	☐☐ age
other cancer	☐	☐☐ age
type of cancer *(please describe)*		
heart disease	☐	☐☐ age
type of heart disease *(please describe)*		
high blood pressure	☐	☐☐ age
stroke	☐	☐☐ age
diabetes	☐	☐☐ age
blood clot (thrombosis)	☐	☐☐ age
enlarged prostate	☐	☐☐ age
asthma	☐	☐☐ age
hayfever	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
Parkinson's disease	☐	☐☐ age
none of these	☐	

25. In the last month have you been treated for:
(If YES, please cross the box and give your age when the treatment started)

	Yes	Age started treatment
cancer	☐	☐☐ age
heart attack or angina	☐	☐☐ age
other heart disease	☐	☐☐ age
high blood pressure	☐	☐☐ age
high blood cholesterol	☐	☐☐ age
blood clotting problems	☐	☐☐ age
asthma	☐	☐☐ age
osteoarthritis	☐	☐☐ age
thyroid problems	☐	☐☐ age
osteoporosis or low bone density	☐	☐☐ age
depression	☐	☐☐ age
anxiety	☐	☐☐ age
none of these	☐	

26. Are you NOW suffering from any other important illness?
☐ Yes ▼ ☐ No

Please describe this illness and its treatment

27. Do you regularly need help with daily tasks because of long-term illness or disability?
(e.g. personal care, getting around, preparing meals)
☐ Yes ☐ No

28. Does your health now LIMIT YOU in any of the following activities?

	yes, limited a lot	**yes**, limited a little	**no**, not limited at all
VIGOROUS activities *(e.g. running, strenuous sports)*	☐	☐	☐
MODERATE activities *(e.g. pushing a vacuum cleaner, playing golf)*	☐	☐	☐
lifting or carrying shopping	☐	☐	☐
climbing several flights of stairs	☐	☐	☐
climbing one flight of stairs	☐	☐	☐
walking one kilometre	☐	☐	☐
walking half a kilometre	☐	☐	☐
walking 100 metres	☐	☐	☐
bending, kneeling or stooping	☐	☐	☐
bathing or dressing yourself	☐	☐	☐

29. Have you ever had any of the following operations?
(If YES, please cross the box and give your age when you had the operation; give your age at the **most recent operation** if you have had more than one)

	Yes	Age when had operation
removal of skin cancer	☐	☐☐ age
vasectomy	☐	☐☐ age
part of prostate removed	☐	☐☐ age
whole prostate removed	☐	☐☐ age
knee replacement	☐	☐☐ age
hip replacement	☐	☐☐ age
gallbladder removed	☐	☐☐ age
heart or coronary bypass surgery *(include stents and balloons)*	☐	☐☐ age

other *(please describe any other operations you have had in the last 10 years, with your age when you had them)*

30. Do you regularly care for a sick or disabled family member or friend?

☐ Yes ▼ ☐ No

If Yes, about how much time each week do you usually spend caring for this person?

☐ full time OR ☐☐ hours/wk

31. In general, how would you rate your:

	excellent	very good	good	fair	poor
overall health?	☐	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐	☐
eyesight? *(with glasses or contact lenses, if you wear them)*	☐	☐	☐	☐	☐
memory?	☐	☐	☐	☐	☐
teeth and gums?	☐	☐	☐	☐	☐

32. Do you feel you have a hearing loss? ☐ Yes ☐ No

33. How many of your own teeth do you have left?

☐ None – all of my teeth are missing ☐ 1-9 teeth left
☐ 10-19 teeth left ☐ 20 or more teeth left

34. During the past 12 months, how many times have you fallen to the floor or ground? (put "0" if you haven't fallen in this time)

☐☐ times

35. Have you had a broken/fractured bone in the last 5 years?

☐ Yes ▼ ☐ No

If Yes, which bones were broken?

☐ wrist ☐ arm ☐ hip ☐ ankle
☐ rib ☐ finger/toe ☐ other_____

How old were you when it happened? (give age at most recent fracture if more than one) ☐☐ years old

36. About how many times a week are you usually troubled by leaking urine?

☐ never ☐ once a week or less ☐ every day
☐ 2-3 times ☐ 4-6 times

37. How often are you able to get and keep an erection that is firm enough for satisfactory sexual activity?

☐ always ☐ usually ☐ sometimes
☐ never ☐ I would rather not answer this question

38. Have you ever had a blood test ordered by your doctor to check for prostate disease? (PSA test)

☐ Yes ▼ ☐ No

If Yes, what year did you have your last PSA test? (e.g. 2005) ☐☐☐☐

How many times have you had a PSA test altogether? ☐☐ times

39. Have you ever been screened for colorectal (bowel) cancer?

☐ Yes ▼ ☐ No

If Yes, please indicate which test(s) you had:

☐ faecal occult blood test *(test for blood in the stool/faeces)*
☐ sigmoidoscopy *(a tube is used to examine the lower bowel: this is usually done in a doctor's office without pain relief)*
☐ colonoscopy *(a long tube is used to examine the whole large bowel; you would usually have to have an enema or drink large amounts of special liquid to prepare the bowel for this)*

What year did you have the most recent one of these tests? (e.g. 2005) ☐☐☐☐

Questions about your diet

40. About how many times each week do you eat: (please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

	number of times eaten each week
beef, lamb or pork	☐☐
chicken, turkey or duck	☐☐
processed meat *(include bacon, sausages, salami, devon, burgers, etc)*	☐☐
fish or seafood	☐☐
cheese	☐☐

41. About how many of the following do you usually eat:

slices or pieces of brown/wholemeal bread each week *(also include multigrain, rye bread, etc.)* ☐☐

bowls of breakfast cereal each week ☐☐

If you eat breakfast cereal is it usually: (please cross)

☐ bran cereal *(allbran, branflakes, etc.)* ☐ muesli
☐ biscuit cereal *(weetbix, shredded wheat, etc.)* ☐ other *(cornflakes, rice bubbles,etc.)*
☐ oat cereal *(porridge, etc.)*

42. Which type of milk do you mostly have?

☐ whole milk ☐ reduced fat milk ☐ skim milk
☐ soy milk ☐ other milk ☐ I don't drink milk

43. About how many serves of vegetables do you usually eat each day? A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)

☐☐ number of serves of cooked vegetables each day
☐☐ number of serves of raw vegetables each day (e.g. salad)
☐ I don't eat vegetables

44. About how many serves of fruit or glasses of fruit juice do you usually have each day? A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)

☐☐ number of serves of fruit each day
☐☐ number of glasses of fruit juice each day
☐ I don't eat fruit

45. Please put a cross in the box if you NEVER eat:

☐ red meat ☐ chicken/poultry ☐ pork/ham ☐ dairy products
☐ any meat ☐ eggs ☐ sugar ☐ wheat products
☐ fish ☐ seafood ☐ cream ☐ cheese

Questions about time and work

46. What is your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation, etc)

☐ less than $5,000 per year ☐ $30,000-$39,999 per year
☐ $5,000-$9,999 per year ☐ $40,000-$49,999 per year
☐ $10,000-$19,999 per year ☐ $50,000-$69,999 per year
☐ $20,000-$29,999 per year ☐ $70,000 or more per year
☐ I would rather not answer this question

47. What is your current work status? (you can cross more than one box)

- ☐ in full time paid work
- ☐ in part time paid work
- ☐ completely retired/pensioner
- ☐ partially retired
- ☐ disabled/sick
- ☐ other
- ☐ self-employed
- ☐ doing unpaid work
- ☐ studying
- ☐ looking after home/family
- ☐ unemployed

48. If you are partially or completely retired, how old were you when you retired? ☐☐ years old

Why did you retire? (you can cross more than one box)

- ☐ reached usual retirement age
- ☐ to care for family member/friend
- ☐ made redundant
- ☐ other
- ☐ lifestyle reasons
- ☐ ill health
- ☐ could not find a job

49. About how many HOURS each WEEK do you usually spend doing the following? (please put "0" if you do not spend any time doing it)

hours per week ☐☐ paid work

hours per week ☐☐ voluntary/unpaid work

50. Which of the following do you have? (excluding Medicare)

- ☐ Private health insurance – with extras
- ☐ Private health insurance – without extras
- ☐ Department of Veterans' Affairs white or gold card
- ☐ Health care concession card
- ☐ none of these

51. What best describes the colour of the skin on the inside of your upper arm, that is your skin colour without any tanning?

- ☐ very fair
- ☐ fair
- ☐ light olive
- ☐ dark olive
- ☐ brown
- ☐ black

52. What would happen if your skin was repeatedly exposed to bright sunlight during summer without any protection? Would it:

- ☐ Get very tanned?
- ☐ Get moderately tanned?
- ☐ Get mildly or occasionally tanned?
- ☐ Never tan, or only get freckled?

53. About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?

hours per day ☐☐ weekday

hours per day ☐☐ weekend

54. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it)

hours per day		hours per day	
☐☐	sleeping (including at night & naps)	☐☐	sitting
☐☐	watching television or using a computer	☐☐	standing

55. How many TIMES in the LAST WEEK did you:
(please put "0" if you did not spend any time doing it)

	times in the last week
spend time with friends or family who do not live with you?	☐☐
talk to someone (friends, relatives or others) on the telephone?	☐☐
go to meetings of social clubs, religious groups or other groups you belong to?	☐☐

56. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to? ☐☐ people

57. During the past 4 weeks, about how often did you feel:

	none of the time	a little of the time	some of the time	most of the time	all of the time
tired out for no good reason?	☐	☐	☐	☐	☐
nervous?	☐	☐	☐	☐	☐
so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
hopeless?	☐	☐	☐	☐	☐
restless or fidgety?	☐	☐	☐	☐	☐
so restless that you could not sit still?	☐	☐	☐	☐	☐
depressed?	☐	☐	☐	☐	☐
that everything was an effort?	☐	☐	☐	☐	☐
so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
worthless?	☐	☐	☐	☐	☐

58. During the past 4 weeks, have you had any of the following problems with your work or daily activities because of any emotional problems (such as being depressed or anxious)?

cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
achieved less than you would have liked to	☐ Yes	☐ No
did work or other activities less carefully than usual	☐ Yes	☐ No

Thank you very much for filling in the questionnaire

DON'T FORGET TO SIGN THE CONSENT FORM OVERLEAF

Are your name and address correct on the front of this questionnaire? ☐ Yes ☐ No

If INCORRECT, give details below.

Surname:

Given name(s):

Postal address:

Town or Suburb:

State or Territory: Postcode:

Consent form

THE 45 AND UP STUDY
Research to improve health and wellbeing

The *45 and Up Study* relies on the willingness of people in New South Wales to share information about their lives and experiences and to have their health followed over time. By signing this form you are agreeing to take part in the *45 and Up Study* and for the Study team to follow your health over time. Participation is completely voluntary, and you are free to ask questions or to withdraw from the Study at any time, by calling the Study helpline on 1300 45 11 45. More information on the Study can be found at www.45andup.org.au

I agree to have my health followed over time through:

the 45 and Up Study team following health and other records relating to me, including NSW hospital records, cancer records, death records and other health-related records, as outlined in the Study leaflet: *The 45 and Up Study: Information for participants*;

Medicare Australia releasing to the 45 and Up Study my enrolment details, including Medicare number, and information concerning services provided to me under Medicare, the Department of Veterans' Affairs, the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme, including past information, until the end of the Study or for the duration of my involvement in the Study;

being contacted in the future to provide information on changes to my health and lifestyle. I may also be asked to provide further information including questionnaire responses or biological samples; my participation in any of these would be completely voluntary.

I give my consent on the understanding that:

my information will only be used for the purposes outlined in the Study leaflet entitled *The 45 and Up Study: Information for participants*, of which I have a copy;

my information will be kept strictly confidential and will be used for health research only;

reports and publications from the Study will be based on de-identified information and will not identify any individual taking part;

my participation in this Study is entirely voluntary and my consent will continue to be valid following death or disablement unless withdrawn by my next of kin or other person responsible. I am free to withdraw from the Study at any time by calling the **Study helpline on 1300 45 11 45;**

my decision on whether or not to take part in the Study or in any additional research will not disadvantage me or affect my future health care in any way.

I have been provided with information about the 45 and Up Study including how it will gather, store, use and disclose information about me, in the Study leaflet. I have been given an opportunity to ask questions and have been fully informed about the Study.

Name (Print): _____

Signature: _____ Date today: day ☐☐ / month ☐☐ / year 2 0 ☐☐

Extra contact details

It would be very helpful and reduce Study costs if we could contact you in future by email. If you are happy for us to do this, please write your email address here:

Email address: _____

Sometimes we find that people have moved when we try to contact them again. It would be very helpful if you could give us your mobile phone number and/or the contact details of someone close to you (such as a relative or friend) who would be happy for us to contact them if we are unable to reach you. We would only get in touch with that person if we were unable to contact you directly and we would need to tell them our reason for contacting you. Please leave this section blank if you do not wish to provide these extra contact details.

Your home phone number: ( ) _____ Your mobile phone number: _____

Full name of contact person: _____

Phone number of contact person: ( ) _____

If you have any questions about the Study, please ring the Study helpline on **1300 45 11 45**.
You can also write to or send your questionnaire (no stamp required) directly to:

Associate Professor Emily Banks, Scientific Director,
The 45 and Up Study, Reply paid 5289, Sydney NSW 2001.

Thank you very much for taking part

Appendix 3 - SEEF Study follow-up questionnaire and consent form

perf

TO BE OVER PRINT mailing info needs to be in 10pt to fit barcode and potential 5 line address in order to gain maximum discount all info must be clearly visible in window with specified clearances around barcode

the saxinstitute

THE 45 AND UP STUDY

Research to improve health and wellbeing

The 45 and Up Study
GPO Box 5289
Sydney NSW 2001
Helpline: 1300 45 11 45
www.45andUp.org.au

<TITLE> <FIRST NAME> <LAST NAME>
<ADDRESS LINE 1>
<ADDRESS LINE 2>
<ADDRESS LINE 3>
<STATE> <POSTCODE>

<DATE>

Dear <FIRST NAME>,

The 45 and Up Study
The SEEF Project

The 45 and Up Study is a long-term health study of over 250,000 people in NSW aged 45 and over. In <MONTH> <YEAR> you agreed to participate in the 45 and Up Study by completing a questionnaire about your health and lifestyle and signing a consent form. By allowing the 45 and Up Study to follow your health over time you are contributing to a better understanding of the major causes of disease and disability in mid to later life. Thank you very much for joining us.

As a participant in the 45 and Up Study, we now seek your involvement in the SEEF Project – a research project that extends the original study to look at how Social, Economic and Environmental Factors (SEEF) contribute to healthy ageing. This project is very large scale, with 100,000 people being asked to assist us, and SEEF will add important information to the 45 and Up Study to help us gain a better understanding of the factors that influence health and wellbeing.

On the other side of this page is an invitation from Professor Adrian Bauman of the School of Public Health at the University of Sydney to participate in the SEEF Project.

If you would like to participate, please complete the questionnaire, sign the consent form, and return it to us in the provided reply paid envelope. More information about the SEEF Project and how to participate is provided in the information pamphlet. You can tear off this letter to keep for your records if desired.

Taking part is entirely your decision, and, if you choose to take part, you can withdraw at any time by calling the 45 and Up Study Helpline on 1300 45 11 45. Your choice will not affect the health care or benefits you receive, or disadvantage you in any way.

Yours sincerely

Professor Emily Banks
Scientific Director, The 45 and Up Study

In partnership with

Cancer Council New South Wales · Heart Foundation · NSW HEALTH · NSW GOVERNMENT Human Services Ageing, Disability & Home · beyondblue · UnitingCare Ageing

perf

THE UNIVERSITY OF SYDNEY

Invitation to join the SEEF Project

Your name has been randomly drawn from the 45 and Up Study participants' list. As a participant in the 45 and Up Study, we now invite you to join the Social, Economic and Environmental Factors (SEEF) Project.

Participation is as easy as completing the confidential questionnaire that follows this letter, signing the consent form giving your permission for us to use the information you have provided, and returning it to us as soon as possible using the enclosed reply paid envelope.

Your participation in this project will only take about 40 minutes of your time and will make a significant contribution to the SEEF Project, which is examining the factors that help our population stay healthy as it ages.

All information given by you to the 45 and Up Study and the SEEF Project will remain completely confidential and used for health research only.

More information about the SEEF Project and the 45 and Up Study more generally is given in the enclosed information pamphlet and on the Study website (www.45andUp.org.au) or you can call the 45 and Up Study Helpline on **1300 45 11 45**. The information pamphlet and this letter can be kept for your own records.

We very much hope that you will be able to take part.

Thank you.

Yours sincerely

Professor Adrian Bauman
Sesquicentenary Professor of Public Health
School of Public Health

THE 45 AND UP STUDY
Research to improve health and wellbeing

THE UNIVERSITY OF SYDNEY

The SEEF Project

Social, Economic and Environmental Factors Questionnaire

The 45 and Up Study relies on the willingness of its participants to share information about their lives and experiences, to provide knowledge that will help people live healthy and fulfilling lives for as long as possible.

This questionnaire looks at which social, economic and environmental factors play a key role in the health and wellbeing of people in the 45 and Up Study.

Participation is completely voluntary, and you are free to withdraw at any time. To take part, please read the participant information leaflet, then complete the questionnaire and consent form and return them in the envelope provided. We very much hope you will be able to take part.

Any questions or comments? Please call the Study Helpline: **1300 45 11 45** or go to **www.45andUp.org.au**

Your answers and experiences are important to us.

To help us read your answers, please use a BLACK or BLUE pen.

Put crosses ☒ OR numbers 7 2 in the appropriate box(es).

General questions about you

1. **What is today's date?**

D D / M M / Y Y Y Y

2. **What is your date of birth?**

D D / M M / Y Y Y Y

3. **What is your gender?** male ☐ female ☐

4. **Have you ever been a regular smoker?** Yes ☐ No ☐ → *Go to* ***Q8***

5. **Are you a regular smoker NOW?** Yes ☐ No ☐ → *Go to* ***Q7***

6. ***If No*** **– how old were you when you stopped smoking regularly?** ☐☐ *years old*

7. **About how much do you/ did you smoke on average each day?** *(if you are an ex-smoker, how much did you smoke on average when you smoked? Leave blank if it does not apply)*

☐☐ *cigarettes per day* ☐☐ *pipes and cigars per day*

8. **About how many alcoholic drinks do you have each week?**
one drink = a glass of wine, middy of beer or nip of spirits
(put "0" if you do not drink, or have less than one drink each week)

☐☐ *number of alcoholic drinks each week*

9. **On how many days each week do you usually drink alcohol?** *(put "0" if you do not drink alcohol)*

☐☐ *days each week*

10. How many TIMES did you do each of these activities LAST WEEK?
(please put "0" if you did not do this activity)

	times in the last week
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*	
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*	
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*	

11. If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?
(please put "0" if you did not do this activity)

	hours	minutes
Walking continuously, for at least 10 minutes *(for recreation or exercise or to get to or from places)*		
Vigorous physical activity *(that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening)*		
Moderate physical activity *(like gentle swimming, social tennis, vigorous gardening or work around the house)*		

12. About how much do you weigh?

kg **OR** *stone* *lbs*

13. About how many serves of vegetables do you usually eat each day? *a serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)*

number of serves of cooked vegetables each day

number of serves of raw vegetables each day (e.g. salad)

☐ I don't eat vegetables

14. About how many serves of fruit or glasses of fruit juice do you usually have each day? *a serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve per day)*

number of serves of fruit each day

number of glasses of fruit juice each day

☐ I don't eat fruit

15. About how many HOURS in each 24 hour DAY do you usually spend doing the following?
(please put "0" if you do not spend any time doing it. The total number of hours does not need to add up to 24)

hours per day		hours per day	
	sleeping (including at night & naps)		*sitting*
	watching television		*standing*
	using a computer		*driving*

16. What is your religious faith or group?
*(please **cross** only one box)*

- ☐ Buddhism
- ☐ Christianity
- ☐ Hinduism
- ☐ Islam
- ☐ Judaism
- ☐ other religions/faith
- ☐ no religion

17. Rate your agreement with the following statement:

	strongly agree	agree	disagree	strongly disagree
I try hard to carry my beliefs over into all other dealings in life	☐	☐	☐	☐

18. Which of these most closely describes your sexual orientation? *(please **cross** only one box)*

- ☐ exclusively heterosexual
- ☐ mainly heterosexual
- ☐ bisexual
- ☐ mainly homosexual (lesbian/gay)
- ☐ exclusively homosexual (lesbian/gay)
- ☐ I don't know
- ☐ I don't want to answer

Questions about you and your household

19. What best describes your current situation?
*(please **cross** only one box)*

- ☐ single
- ☐ widowed
- ☐ married
- ☐ divorced
- ☐ de facto/living with partner
- ☐ separated

20. Including yourself, how many people in total live in your household? *(put "1" if you live alone)*

21. How many financially dependent children do you have aged:
(put "0" if you have no dependents)

under 15 years old?

15-24 years old?

22. What best describes your current housing or family home?
*(please **cross** only one box)*

- ☐ house
- ☐ hostel for the aged
- ☐ nursing home
- ☐ flat, unit, apartment
- ☐ mobile home
- ☐ retirement village, self care unit
- ☐ house on farm
- ☐ other

23. Do you (or any other members of this household) own this home, rent it, or do you live here rent free?

- ☐ own
- ☐ currently paying off mortgage/ involved in a rent-buy scheme
- ☐ rent (or pay board)
- ☐ live here rent free/ life tenure

24. Do you currently own (or are paying off mortgage for) any other property that you do not live in? Yes ☐ No ☐

25. In the past year, at times my house/apartment has felt:
*(please **cross** as many as apply)*

- ☐ so cold that I have had trouble sleeping
- ☐ so hot that I have had trouble sleeping
- ☐ so cold that I have had trouble going about my normal activities
- ☐ so hot that I have had trouble going about my normal activities
- ☐ comfortable
- ☐ none of the above

26. How is your house/apartment cooled?
*(please **cross** only one box)*

- ☐ no cooling system
- ☐ central (ducted) air conditioning
- ☐ room air conditioning
- ☐ evaporative air conditioning

27. What is your MAIN source of drinking water at home?
*(please **cross** only one box)*

- ☐ public water supply
- ☐ bottled water
- ☐ rainwater
- ☐ private bore, spring or well
- ☐ other private water supply
- ☐ combination of different water sources
- ☐ other (specify)

28. During the past 5 years, have you changed your main source of drinking water due to:

	Yes	No
drought?	☐	☐
poor water quality?	☐	☐

29. How many motor vehicles in working order are there at your household?

☐☐ *vehicles*

Questions about your health

30. In general, how would you rate your:

	excellent	very good	good	fair	poor
overall health?	☐	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐	☐
eyesight? (with glasses or contact lenses, if you wear them)	☐	☐	☐	☐	☐
hearing?	☐	☐	☐	☐	☐
memory?	☐	☐	☐	☐	☐
teeth and gums?	☐	☐	☐	☐	☐

31. Do you regularly need help with daily tasks because of long-term illness or disability? *(e.g. personal care, getting around, preparing meals)* Yes ☐ No ☐

32. Do you ever need someone to help with, or be with you for, self care activities? *(e.g. doing everyday activities such as eating, showering, dressing or toileting)* Yes ☐ No ☐

33. Do you ever need someone to help with, or be with you for, body movement activities?
(e.g. getting out of bed, moving around at home or at places away from home) Yes ☐ No ☐

34. Do you ever need someone to help with or be with you for, communication activities?
(e.g. understanding, or being understood by others) Yes ☐ No ☐

35. During the past 12 months, how many times have you fallen to the floor or ground?
(put "0" if you haven't fallen in this time)

☐☐ *times*

36. Have you had a broken/fractured bone in the last 3 years? Yes ☐ No ☐

→ *Go to **Q37***

***If YES*, which bones were broken?**

- ☐ wrist
- ☐ arm
- ☐ hip
- ☐ ankle
- ☐ rib
- ☐ finger/toe
- ☐ other (specify)

How old were you when it happened?
(give age at most recent fracture if more than one)

☐☐ *years old*

Reflex Blue Pantone 346

37. Has a doctor EVER told you that you have:
*(if YES, please **cross** the box and give your age when the condition was first found)*

	Yes	age when condition was first found
skin cancer *(not melanoma)*	☐	age
melanoma	☐	age
breast cancer	☐	age
prostate cancer *(men only)*	☐	age
other cancer	☐	age

type of cancer *(please describe)*

heart disease	☐	age

type of heart disease *(please describe)*

high blood pressure *(women only – when pregnant)*	☐	age
high blood pressure *(women only – when not pregnant)*	☐	age
high blood pressure *(men only)*	☐	age
stroke	☐	age
diabetes	☐	age
blood clot *(thrombosis)*	☐	age
enlarged prostate *(men only)*	☐	age
asthma	☐	age
hayfever	☐	age
depression	☐	age
anxiety	☐	age
Parkinson's disease	☐	age
chronic kidney disease	☐	age
none of these	☐	

38. In the last month have you been treated for:
*(if YES, please **cross** the box and give your age when the treatment started)*

	Yes	age started treatment
cancer	☐	age
heart attack or angina	☐	age
other heart disease	☐	age
high blood pressure	☐	age
high blood cholesterol	☐	age
blood clotting problems	☐	age
asthma	☐	age
osteoarthritis	☐	age
thyroid problems	☐	age
osteoporosis or low bone density	☐	age
depression	☐	age
anxiety	☐	age
none of these	☐	

39. Are you NOW suffering from any other important illness? Yes ☐ No ☐

please describe this illness and its treatment

40. Have you ever been screened for colorectal (bowel) cancer? Yes ☐ No ☐

→ *Go to **Q41***

***If YES*, please indicate which test(s) you had:**

- ☐ faecal occult blood test *(test for blood in the stool/faeces)*
- ☐ sigmoidoscopy *(a tube is used to examine the lower bowel; this is usually done in a doctor's office without pain relief)*
- ☐ colonoscopy *(a long tube is used to examine the whole large bowel; you would usually have to have an enema or drink large amounts of special liquid to prepare the bowel for this)*

What year did you have the most recent one of these tests? (*eg. 2005*) Y Y Y Y

41. About how many times a week are you usually troubled by leaking urine?

- ☐ never
- ☐ once a week or less
- ☐ 2-3 times
- ☐ 4-6 times
- ☐ every day

42. Do you regularly care for a sick or disabled family member or friend? Yes ☐ No ☐

→ *Go to* ***Q44***

If YES, **about how much time each week do you usually spend caring for this person?**

☐ full time **OR** ☐☐☐ *hours/wk*

43. Do you live with the person you care for? Yes ☐ No ☐

44. Does your health now LIMIT YOU in any of the following activities?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
VIGOROUS activities (e.g. running, strenuous sports)	☐	☐	☐
MODERATE activities (e.g. pushing a vacuum cleaner, playing golf)	☐	☐	☐
lifting or carrying shopping	☐	☐	☐
climbing several flights of stairs	☐	☐	☐
climbing one flight of stairs	☐	☐	☐
walking one kilometre	☐	☐	☐
walking half a kilometre	☐	☐	☐
walking 100 metres	☐	☐	☐
bending, kneeling or stooping	☐	☐	☐
bathing or dressing yourself	☐	☐	☐

45. During the past 4 weeks, have you:

	Yes	No
accomplished less than you would like in your regular daily activities because of your physical health?	☐	☐
been limited in your regular activities because of your physical health?	☐	☐
accomplished less than you would like as a result of any emotional problems?	☐	☐
not done work or other regular activities as carefully as usual as a result of any emotional problems?	☐	☐

46. During the past 4 weeks, how much did pain interfere with your normal work, including outside the home and housework?

- ☐ not at all
- ☐ slightly
- ☐ moderately
- ☐ quite a bit
- ☐ extremely

47. How much time during the past 4 weeks:

	none of the time	a little of the time	some of the time	most of the time	all of the time
have you felt calm and peaceful?	☐	☐	☐	☐	☐
did you have a lot of energy?	☐	☐	☐	☐	☐
have you felt down?	☐	☐	☐	☐	☐
have your physical health or emotional problems interfered with your social activities?	☐	☐	☐	☐	☐

48. During the past 4 weeks, about how often did you feel:

	none of the time	a little of the time	some of the time	most of the time	all of the time
tired out for no good reason?	☐	☐	☐	☐	☐
nervous?	☐	☐	☐	☐	☐
so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
hopeless?	☐	☐	☐	☐	☐
restless or fidgety?	☐	☐	☐	☐	☐
so restless that you could not sit still?	☐	☐	☐	☐	☐
depressed?	☐	☐	☐	☐	☐
that everything was an effort?	☐	☐	☐	☐	☐
so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
worthless?	☐	☐	☐	☐	☐

49. Thinking of times when you want to see a particular doctor in your practice or medical centre, how quickly do you usually get to see that doctor?

- ☐ same day
- ☐ next day
- ☐ 2-3 days
- ☐ 4-5 days
- ☐ more than 5 days

50. Thinking of times when you are willing to see ANY doctor in your practice or medical centre, how quickly do you usually get seen by any doctor?

- ☐ same day
- ☐ next day
- ☐ 2-3 days
- ☐ 4-5 days
- ☐ more than 5 days

51. If you need to see a GP urgently, can you normally get seen on the same day? Yes ☐ No ☐

(leave blank if question does not apply)

52. **In the past 2 years, have you needed to see any specialist doctors?** Yes ☐ No ☐ → *Go to* ***Q54***

53. **After learning you needed to see a specialist doctor(s), how long on average did you have to wait for an appointment?**

- ☐ no waiting period
- ☐ less than a week
- ☐ 1-2 weeks
- ☐ 3-4 weeks
- ☐ 5-8 weeks
- ☐ more than 8 weeks

54. **How long does it take you to travel to your usual or preferred GP?**

- ☐ < 30 minutes
- ☐ 30-59 minutes
- ☐ 1-2 hours
- ☐ 2-3 hours
- ☐ 3-4 hours
- ☐ 4 or more hours
- ☐ doctor visits me

55. **How long does it take you to travel to the nearest hospital?**

- ☐ < 30 minutes
- ☐ 30-59 minutes
- ☐ 1-2 hours
- ☐ 2-3 hours
- ☐ 3-4 hours
- ☐ 4 or more hours

56. **In the past 12 months, about how much have you and your household spent out-of-pocket for medical treatments or services that were NOT covered by Medicare or private insurance?** *(include costs for prescription medicines and tests or treatments by a doctor or health professional, including any gap payment or any items not covered)*

- ☐ none
- ☐ $1-$250
- ☐ $251-$500
- ☐ $501-$1,000
- ☐ $1,001-$2,000
- ☐ more than $2,000

57. **In the past 12 months, have you:**

	Yes	No
received a blood pressure check?	☐	☐
had your cholesterol checked?	☐	☐
had your skin checked for cancer?	☐	☐
had a blood test to check your sugar levels?	☐	☐
been told by your GP to eat fewer high fat or high cholesterol foods?	☐	☐
been told by your GP to eat more fruits & vegetables?	☐	☐
been told by your GP to be more physically active?	☐	☐
been told by your GP to quit smoking?	☐	☐

58. **On a scale from 1 to 10, how confident are you that you can do all the things necessary to manage your health on a regular basis?** *(**cross** one number only)*

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

not at all confident … **totally confident**

59. **On a scale from 1 to 10, how confident are you that you can judge when the changes in your health mean you should visit a doctor?** *(**cross** one number only)*

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

not at all confident … **totally confident**

Questions about work and income

Some of these questions ask for details of your economic circumstances. We are asking these because economic and financial factors are important for health.

Remember you do not have to answer any questions if you do not want to and all information will be kept strictly confidential and used for health related research only.

60. **What is your usual yearly HOUSEHOLD income before tax, from all sources?** *(please include wages benefits, pensions, superannuation, etc)*

- ☐ less than $5,000
- ☐ $5,000-$9,999
- ☐ $10,000-$19,999
- ☐ $20,000-$29,999
- ☐ $30,000-$39,999
- ☐ $40,000-$49,999
- ☐ $50,000-$59,999
- ☐ $60,000-$69,999
- ☐ $70,000-$79,999
- ☐ $80,000-$89,999
- ☐ $90,000-$119,999
- ☐ $120,000-$149,999
- ☐ $150,000 or more
- ☐ I would rather not answer this question

61. **What is your usual PERSONAL yearly income before tax, from all sources?** *(please include wages, benefits, pensions, superannuation etc)*

- ☐ less than $5,000
- ☐ $5,000-$9,999
- ☐ $10,000-$19,999
- ☐ $20,000-$29,999
- ☐ $30,000-$39,999
- ☐ $40,000-$49,999
- ☐ $50,000-$59,999
- ☐ $60,000-$69,999
- ☐ $70,000-$79,999
- ☐ $80,000-$89,999
- ☐ $90,000-$119,999
- ☐ $120,000-$149,999
- ☐ $150,000 or more
- ☐ I would rather not answer this question

62. **What is your current work status?** *(you can **cross** more than one box)*

- ☐ in full time paid work
- ☐ in part time paid work
- ☐ completely retired/ pensioner
- ☐ partially retired
- ☐ disabled/sick
- ☐ self-employed
- ☐ doing unpaid work
- ☐ studying
- ☐ looking after home/family
- ☐ unemployed
- ☐ other

63. About how many HOURS each WEEK do you and your partner usually spend in paid work?
(please put "0" if you do not spend any time doing it)

YOU	YOUR PARTNER
hours per week paid work	*hours per week paid work*

☐ I do not have a partner

64. If you are partially or completely retired or not working for another reason, how old were you when you retired or stopped work?

years old

Why did you retire/stop work?
*(you can **cross** more than one box)*

- ☐ reached usual retirement age
- ☐ to care for sick/disabled person
- ☐ to look after home/family
- ☐ made redundant
- ☐ could not find a job
- ☐ was self-employed & business closed
- ☐ lifestyle reasons
- ☐ work-related injury
- ☐ own ill health
- ☐ to travel
- ☐ to study
- ☐ other

65. If you retired due to your own ill health, what was the main health condition leading to your retirement?
*(please **cross** only one box)*

- ☐ arthritis
- ☐ asthma
- ☐ back problems
- ☐ cancer
- ☐ diabetes
- ☐ digestive system diseases
- ☐ diseases of the nervous system *(e.g. Parkinson's disease)*
- ☐ eye diseases *(e.g. cataracts)*
- ☐ other condition *(specify):*
- ☐ heart disease/stroke
- ☐ injury – work-related
- ☐ injury – non-work related
- ☐ mental disorders
- ☐ respiratory system diseases
- ☐ other musculoskeletal condition *(e.g. osteoporosis)*

66. Is your partner retired?

Yes	No	No partner
☐	☐	☐

***If Yes*, age s/he retired?** *age*

67. Over the last 12 months did any of the following happen to you because of a shortage of money?

	Yes	No
could not fill or collect a prescription medicine	☐	☐
could not get a medical test, treatment, or follow-up that was recommended by a doctor	☐	☐
limited how much fruit and/or vegetables you eat	☐	☐
could not pay electricity, gas or telephone bills on time	☐	☐
could not pay the mortgage or rent on time	☐	☐
asked for financial help from friends or family	☐	☐

Questions about social support

68. Rate how often the following occur:

	never	rarely	some times	often	always	N/A*
Your partner makes you feel cared for	☐	☐	☐	☐	☐	☐
Your partner makes too many demands on you	☐	☐	☐	☐	☐	☐
Other family members make you feel cared for	☐	☐	☐	☐	☐	☐
Other family members make too many demands on you	☐	☐	☐	☐	☐	☐
Friends make you feel cared for	☐	☐	☐	☐	☐	☐
Friends make too many demands on you	☐	☐	☐	☐	☐	☐

**** N/A – Not Applicable or do not have partner/family members/friends***

69. Rate how often the following occur:

	never	rarely	some times	often	always	N/A*
Co-workers make you feel cared for	☐	☐	☐	☐	☐	☐
Co-workers make too many demands on you	☐	☐	☐	☐	☐	☐
Co-workers express interest in how you are doing	☐	☐	☐	☐	☐	☐
Co-workers criticise you	☐	☐	☐	☐	☐	☐
Co-workers create tensions or have arguments with you	☐	☐	☐	☐	☐	☐

N/A – Not Applicable or not in working environment

70. How often do you feel rushed or pressed for time?

never	rarely	some times	often	always
☐	☐	☐	☐	☐

71. How many TIMES in the LAST WEEK did you:
(please put "0" if you did not spend any time doing it)

	times in the last week
spend time with friends or family who do not live with you?	
talk to someone (friends, relatives or other personal calls) on the telephone?	
go to meetings of social clubs, religious groups or other groups you belong to?	
spend time in internet social activities? *(e.g. social network sites)*	

72. How many people outside your home, but within one hour of travel, do you feel you can depend on or feel very close to?

people

73. In the past 12 MONTHS have any of the following been a problem for you or anyone close to you?
*(you can **cross** more than one box)*

- ☐ serious illness
- ☐ serious accident
- ☐ serious disability
- ☐ mental illness
- ☐ divorce or separation
- ☐ not able to get a job
- ☐ involuntary loss of job
- ☐ alcohol or drug-related problems
- ☐ gambling problem
- ☐ witness to violence
- ☐ abuse or violent crime
- ☐ trouble with the police
- ☐ death of a family member or close friend
- ☐ none of these

Questions about your neighbourhood

74. Answer YES or NO to the following questions:

	Yes	No
do you go outside your local area to visit your family?	☐	☐
can you get help from friends when you need it?	☐	☐
if you were caring for someone and needed to go out for a while, would you ask a neighbour for help?	☐	☐
have you visited a neighbour in the past week?	☐	☐
when you shop in your local area are you likely to run into friends and acquaintances?	☐	☐
in the past 6 months, have you done a favour for a sick neighbour?	☐	☐
do you agree that most people in your neighbourhood can be trusted?	☐	☐
does your area have a reputation for being a safe place?	☐	☐

75. Rate your agreement with the following statement:

	strongly agree	agree	disagree	strongly disagree
many shops, stores, markets or other places to buy things I need are within easy walking distance of my home	☐	☐	☐	☐
a public transport stop (such as a bus or train) is within a 10-15 minute walk from my home	☐	☐	☐	☐
there are footpaths on most of the streets in my neighbourhood	☐	☐	☐	☐
my neighbourhood has several free or low cost recreation facilities, such as parks, walking paths, swimming pools, etc	☐	☐	☐	☐

75. *continued.* **Rate your agreement with the following statements:**

	strongly agree	agree	disagree	strongly disagree
the crime rate in my neighbourhood makes it unsafe to go on walks at NIGHT	☐	☐	☐	☐
the crime rate in my neighbourhood makes it unsafe to go on walks during the DAY	☐	☐	☐	☐

76. How long have you lived at your current address? ☐☐ *years*

77. List the state, postcode or suburb, and time period for your last <u>two</u> places of residence in AUSTRALIA

77a. What was your most recent PREVIOUS residential location?

Postcode: ☐☐☐☐ OR

Suburb/Town:

State/Territory:

☐ ACT ☐ SA
☐ NSW ☐ TAS
☐ NT ☐ VIC
☐ QLD ☐ WA
☐ OVERSEAS

If overseas, country:

How long did you live there?

☐☐ *years* OR ☐☐ *months*

77b. Where did you live IMMEDIATELY before that?

Postcode: ☐☐☐☐ OR

Suburb/Town:

State/Territory:

☐ ACT ☐ SA
☐ NSW ☐ TAS
☐ NT ☐ VIC
☐ QLD ☐ WA
☐ OVERSEAS

If overseas, country:

How long did you live there?

☐☐ *years* OR ☐☐ *months*

78. List the state, the postcode or suburb, and time period of employment for your last <u>two</u> places of employment in AUSTRALIA

78a. What was your most recent PREVIOUS employment location?

Postcode: ☐☐☐☐ OR

Suburb/Town:

State/Territory:

☐ ACT ☐ SA
☐ NSW ☐ TAS
☐ NT ☐ VIC
☐ QLD ☐ WA
☐ OVERSEAS

If overseas, country:

How long did you work there?

☐☐ *years* OR ☐☐ *months*

78b. Where did you work IMMEDIATELY before that?

Postcode: ☐☐☐☐ OR

Suburb/Town:

State/Territory:

☐ ACT ☐ SA
☐ NSW ☐ TAS
☐ NT ☐ VIC
☐ QLD ☐ WA
☐ OVERSEAS

If overseas, country:

How long did you work there?

☐☐ *years* OR ☐☐ *months*

Don't forget to sign the consent form overleaf.

Please return your completed questionnaire in the envelope provided. No stamp is required.

THE 45 AND UP STUDY

Research to improve health and wellbeing

THE UNIVERSITY OF SYDNEY

Consent Form - The SEEF Project

The 45 and Up Study is designed to provide much needed information about how to stay healthy and independent throughout life. As one of over 250,000 45 and Up Study participants, you have already completed a questionnaire about your health and lifestyle.

We are asking for your help again to give additional information about your health and the social, economic and environmental factors that impact on healthy ageing by completing a questionnaire for the SEEF Project.

By signing this consent form you are agreeing to participate in the SEEF Project, as outlined in the participant information leaflet entitled *"The SEEF Project – Information for Participants"*.

Participation in the SEEF Project is entirely voluntary and you may ask questions or withdraw your consent at any time by calling the 45 and Up Study Helpline on 1300 45 11 45.

In signing this consent form, I agree:

- To the 45 and Up Study providing my questionnaire to the researchers of the SEEF Project.
- To the long-term storage and use of the information from my questionnaire for health-related research.
- To the 45 and Up Study combining the new information from my questionnaire with the information I have already given to the 45 and Up Study, as outlined in the participant information leaflet entitled *"The SEEF Project – Information for Participants"* of which I have a copy.

I give my consent on the understanding that:

- My information will only be used for the purposed outlined in the participant information leaflet entitled *"The SEEF Project – Information for Participants"*.
- My information will be kept strictly confidential and will be used for health research only. Research, reports and publications from the 45 and Up Study and the SEEF Project will be based on de-identified information and will not identify any individual taking part.
- My consent will continue to be valid following death or loss of decision-making capacity unless withdrawn by my next of kin or other person responsible. I may withdraw from the 45 and Up Study or the SEEF Project at any time by calling the 45 and Up Study Helpline on 1300 45 11 45.
- My decision as to whether or not to participate in the SEEF Project or any other additional research will not disadvantage me or affect my future healthcare in any way.
- I may be contacted again by the 45 and Up Study regarding future research, and my participation in this will be entirely voluntary.

I have read all of the above, as well as the information provided in the participant information leaflet entitled *"The SEEF Project – Information for Participants"*. I have been given the opportunity to ask questions and have been fully informed about the SEEF Project. I agree to participate in the SEEF Project.

Name (Print):

Signature:

Date today: D D / M M / Y Y Y Y

Extra contact details:

It would be very helpful and reduce study costs if we could contact you in future by email. If you are happy for us to do this, please print your email address here:

Email address:

Have you changed your address? Please let us know your new details:

Surname:

Given name(s):

Postal address:

Town or Suburb: *State or Territory:* *Postcode:*

Thank you very much for filling in the questionnaire.

If you have any questions, please ring the 45 and Up Study Helpline on **1300 45 11 45.**
You can also write directly to:
Professor Emily Banks, Scientific Director
The 45 and Up Study
GPO Box 5289, Sydney NSW 2001

Please send your questionnaire (no stamp required) to:
Confidential
The 45 and Up Study
The SEEF Project
Reply Paid 1005
BROADWAY NSW 2007

Appendix 4 - Additional research dissemination arising from this thesis

UNIVERSITY OF SYDNEY 3 MINUTE THESIS COMPETITION

Nguyen B. Exploring novel lifestyle risk factors for heart disease in women.

School of Public Health heat winner

Faculty of Medicine heat finalist

Appendix 5 - Additional publications

Additional peer-reviewed papers outside the scope of my thesis, for which I was the lead author or a co-author during my PhD candidature, are listed below.

List of additional published peer-reviewed papers

Nguyen B, Ding D, Mihrshahi S. Fruit and vegetable consumption and psychological distress: cross-sectional and longitudinal analyses based on a large Australian sample. *BMJ Open* 2017; 7: e014201. Available from: http://doi.org/10.1136/bmjopen-2016-014201

Ding D, Kolbe-Alexander T, Nguyen B, Katzmarzyk PT, Pratt M, Lawson KD. The economic burden of physical inactivity: a systematic review and critical appraisal. *British Journal of Sports Medicine* 2017; 51 (19): 1392-1409. Available from: http://doi.org/10.1136/bjsports-2016-097385

Mihrshahi S, Foley B, Nguyen B, Gander K, Tan N, Hudson N, et al. Evaluation of the Cancer Council NSW *Eat It To Beat It Healthy Lunch Box* Sessions: A short intervention to promote the intake of fruit and vegetables among families of primary school children in NSW Australia. *Health Promotion Journal of Australia* 2017; 00: 1-6. Available from: http://doi.org/10.1002/hpja.23

Ding D, Nguyen B, Learnihan V, Bauman AE, Davey R, Jalaludin B, et al. Moving to an active lifestyle? A systematic review of the effects of residential relocation on walking, physical activity and travel behaviour. *British Journal of Sports Medicine* 2018; 52: 789-799. Available from: http://doi.org/10.1136/bjsports-2017-098833

BMJ Open

Fruit and vegetable consumption and psychological distress: cross-sectional and longitudinal analyses based on a large Australian sample

Binh Nguyen, Ding Ding, Seema Mihrshahi

To cite: Nguyen B, Ding D, Mihrshahi S. Fruit and vegetable consumption and psychological distress: cross-sectional and longitudinal analyses based on a large Australian sample. *BMJ Open* 2017;**7**:e014201. doi:10.1136/bmjopen-2016-014201

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-014201).

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ABSTRACT

Objectives: Growing evidence suggests a link between diet and mental health. This study aimed to investigate the association between fruit and vegetable consumption and the prevalence and incidence of psychological distress in middle-aged and older Australians.

Design: Cross-sectional and prospective.

Setting: New South Wales, Australia.

Methods: A sample of 60 404 adults aged ≥45 years completed baseline (2006–2008) and follow-up (2010) questionnaires. Psychological distress was assessed at baseline and follow-up using the validated Kessler Psychological Distress Scale (K10), a 10-item questionnaire measuring general anxiety and depression. Psychological distress was defined as the presence of high-to-very high levels of distress (K10 score ≥22). Usual fruit and vegetable consumption was assessed using short validated questions. The association between baseline fruit and vegetable consumption and the prevalence or incidence of psychological distress was examined using logistic regression models.

Results: At baseline, 5.6% reported psychological distress. After a mean 2.7 years of follow-up, 4.0% of those who did not report distress at baseline reported distress at follow-up. Baseline fruit and vegetable consumption considered separately or combined, was associated with a lower prevalence of psychological distress even after adjustment for sociodemographic characteristics and lifestyle risk factors. Baseline fruit and vegetable consumption, measured separately or combined, was associated with a lower incidence of psychological distress in minimally adjusted models. Most of these associations remained significant at medium levels of intake but were no longer significant at the highest intake levels in fully adjusted models.

Conclusions: Increasing fruit and vegetable consumption may help reduce psychological distress in middle-aged and older adults. However, the association of fruit and vegetable consumption with the incidence of psychological distress requires further investigation, including the possibility of a threshold effect between medium and higher consumption levels.

Strengths and limitations of this study

- This study included a large sample size of 60 404 participants for cross-sectional analyses and 54 345 participants for longitudinal analyses.
- Analyses were adjusted for multiple sociodemographic and lifestyle-related covariates.
- The well-validated Kessler Psychological Distress Scale (K10) was used to assess psychological distress.
- The relatively short follow-up time may have been insufficient to observe the full extent of long-term associations between fruit and vegetable intake and psychological distress.

INTRODUCTION

There has been a global call for action by the WHO to make mental health a global development priority.[1] Mental disorders affect a 10th of the world population and represent 30% of non-fatal global burden of disease.[2] Depression alone is a leading cause of disability worldwide[3] and is projected to rank among the three leading causes of global disease burden by 2030.[4] There is an urgent call for public health strategies aimed at preventing the onset on common mental disorders, such as depression.

There has been considerable interest in the relationship between psychological well-being and lifestyle factors, with growing evidence for a link between mental health and diet.[5–7] The role of fruit and vegetables has received increasing attention, given evidence for its protective effects against chronic diseases such as cardiovascular disease and cancer.[8 9] Diets low in fruit have been recently identified as the leading dietary risk factor for global burden of disease.[10]

Findings from a recent meta-analysis, based on seven cross-sectional and four prospective studies, suggest that both fruit and

vegetable consumption are significantly associated with a lower risk of depression.[11] Several large cross-sectional studies have shown that greater consumption of fruit and vegetables is associated with better mental health, including lower odds of depression and psychological distress, in the general population.[12–14] Fewer studies have investigated the longitudinal association between fruit and vegetable intake and depression. Higher consumption of fruit and/or vegetables was associated with lower odds of incident depression in middle-aged Australian women followed over 6 years,[15] postmenopausal American women followed for 3 years[16] and Spanish adults followed over 4 years.[17] These findings are in agreement with previous cross-sectional and longitudinal studies that have found healthy dietary patterns, including high intakes of fruit and vegetables, to be associated with a lower risk of depression and anxiety, particularly in middle-aged and older adults.[18–21]

Depression in later life is associated with increased morbidity and mortality, and decreased physical, cognitive and social functioning.[22] Improving mental health is an important public health challenge to address in an ageing population with a higher life expectancy.[1] Therefore, the main objective of this study was to investigate the association between fruit and vegetable consumption and the prevalence and incidence of psychological distress in a large cohort of middle-aged and older Australians.

METHODS

Study population

The baseline data were from the Sax Institute's 45 and Up Study, a large-scale (n=267 153) population study of men and women aged 45 years and over, who were randomly sampled from the general population of New South Wales (NSW), Australia. From January 2006 to December 2008, eligible individuals joined the study by completing a postal questionnaire and providing written consent for participation and long-term follow-up. The 45 and Up Study has been described in detail elsewhere.[23] A subsample of the 45 and Up Study was followed up in 2010 (ie, the Social, Economic, and Environmental Factor (SEEF) Study), with the first 100 000 participants of the 45 and Up Study invited to complete the SEEF questionnaire (60.4% response rate). A participant flow chart for this study is provided in figure 1. For cross-sectional analyses at baseline, the analytic sample included 60 404 participants (53.6% women). For longitudinal analyses, participants who reported on the baseline questionnaire that they had been treated for depression/anxiety in the previous month (n=3796), and/or taking antidepressant medication for most of the past 4 weeks (n=700), and/or with high/very high levels of psychological distress (n=3030; defined as having a Kessler Psychological Distress Scale (K10) score ≥22[24] were excluded (n=6067), leaving a final sample of 54 345 participants.

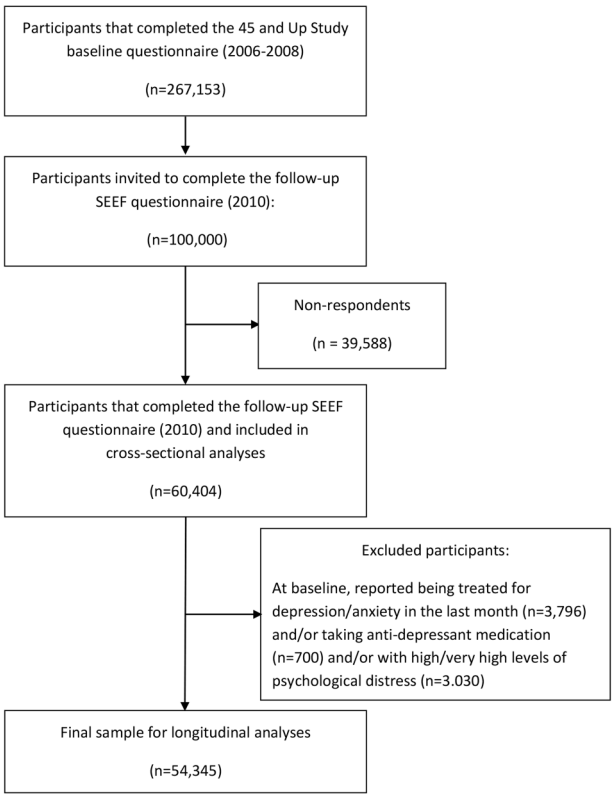

Figure 1 Participant flow chart. SEEF, Social, Economic, and Environmental Factor.

Measurement

The 45 and Up Study and SEEF Study questionnaires include questions on sociodemographic characteristics, personal and medical history, and lifestyle risk factors (available from http://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/).

Outcome

At both baseline and follow-up, participants' general level of psychological distress was assessed using the well-validated and widely used K10, a 10-item questionnaire about anxiety and depression symptoms experienced in the past 4 weeks.[24] A five-point response scale (none of the time, a little of the time, some of the time, most of the time, all of the time) is used for each item, with scores ranging from 1 (none of the time) to 5 (all of the time). Scores to each question are added up to form the total K10 score, with a possible range of 10–50. For this study, score groupings and categories of psychological distress routinely used by the Australian Bureau of Statistics for national health surveys were adopted with total scores of: 10–15, 16–21, 22–29 and 30–50 indicating low, moderate, high and very high levels of psychological distress, respectively.

High K10 scores are strongly correlated with current WHO's Composite International Diagnostic Interview (CIDI) diagnosis of anxiety and affective disorders.[24] Prevalence of psychological distress at baseline was

defined as the presence of high-to-very high levels of psychological distress (K10 score ≥22). Incidence of psychological distress was defined as: (1) not being treated for anxiety/depression in the previous month, and/or not taking antidepressant medication for most of the past 4 weeks, and/or not having high/very high levels of psychological distress (K10 score <22) at baseline, and (2) the presence of high-to-very high levels of psychological distress (K10 score ≥22) at follow-up. Psychological distress was treated as binary outcome variable in the analyses (K10 score <22 vs ≥22; ie, low-to-moderate vs high-to-very high levels of distress).

Exposure

Usual fruit and vegetable consumption was assessed at baseline using the following validated short questions commonly used in health monitoring and surveillance:[25]

1. 'About how many serves of fruit do you usually have each day?' One serve of fruit was defined as one medium piece or two small pieces of fresh fruit, or one cup of diced or canned fruit pieces.
2. 'About how many serves of vegetables do you usually eat each day?' One serve of vegetables was defined as half a cup of cooked vegetables (including potatoes) or one cup of raw vegetables (eg, salad).

Total fruit and vegetable consumption was derived by summing the reported number of fruit and vegetables consumed daily. Fruit and vegetable consumption, considered separately and combined, was categorised into tertiles. Using quantiles ensures that the range in exposure is captured evenly across distribution categories, which facilitates comparison between different levels of fruit and vegetable consumption among the study cohort, and has been previously used in another large cohort study.[16]

Covariates

Covariates included baseline self-reported sociodemographic characteristics such as sex, age, highest level of education (≤10 years of schooling, high school/trade apprenticeship/certificate/diploma, university degree/higher), marital status (married/living with a partner vs single/widowed/divorced/separated), household annual income (<$30 000, $30 000–$69 999, ≥$70 000, would rather not answer this question), self-reported history of major chronic disease (cancer other than non-melanoma skin cancer, cardiovascular disease (heart disease, stroke or blood clot), diabetes or hypertension; yes vs no) and the following lifestyle risk factors: body mass index (BMI; derived from self-reported height and weight; defined as underweight ((<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight/obese (≥25 kg/m^2)), alcohol intake (≤14 or >14 drinks/week), smoking status (current regular smoker vs not currently a regular smoker) and physical activity levels (assessed using validated questions from the Active Australia Survey;[26] categorised as <150, 150–299 and ≥300 min/week).

Statistical analysis

The association between baseline fruit and vegetable consumption and the prevalence/incidence of psychological distress (K10 score ≥22) was examined using logistic regression models. ORs with 95% CIs are presented for unadjusted, age-adjusted and sex-adjusted, and models adjusted for all covariates as described above. We tested effect modification by sex by fitting interaction terms. To examine potential sex differences, the analyses were further stratified by sex. If 1 out of 10 responses to K10 questions was missing (for 3.2% and 2.8% of participants included in cross-sectional and longitudinal analyses, respectively), the missing value was imputed using the mean score across the other 9 questions.[27] If more than one response was missing, K10 scores were considered as missing. p Values <0.05 were considered statistically significant. All analyses were conducted using SPSS V.22 (IBM Corp, Armonk, New York, USA).

RESULTS

Participant characteristics

Table 1 shows baseline participant characteristics based on K10 score at follow-up. Overall, the mean age (SD) of participants was 62.2 (10.6) years, more than half (53.6%) were women, over a quarter (26%) had a university degree/higher, over three-quarters (78%) were in a married/de facto relationship, and a quarter (25.7%) reported a household annual income ≥$70 000. The mean (SD) serves of fruit and vegetables were, respectively, 2.0 (1.4) and 3.9 (2.6) serves/day. The average follow-up time period was 2.7 (0.9) years. Compared with men, women were more likely to be younger, less educated, single/widowed/divorced/separated, have a lower household annual income, a lower BMI, and to consume more fruit and vegetables and less alcohol. Participants with high-to-very high levels of psychological distress (5.6%) at baseline were more likely to be women, relatively younger, less educated and have a lower household annual income. These participants were also more likely to: have a higher BMI, be a current smoker, be less physically active and have a history of chronic disease.

Prevalence of psychological distress

The ORs for the association between separate or combined fruit and vegetable consumption and the prevalence of high-to-very high levels of psychological distress (K10≥22) are presented in table 2. Consumption of fruit and vegetables, considered separately or combined, was consistently associated with a lower prevalence of psychological distress. Following adjustment for all covariates, these associations were slightly attenuated compared with the unadjusted model but remained significant. Other covariates which were significantly associated with the prevalence of psychological distress were being relatively younger, single/divorced/widowed/separated, a

Table 1 Baseline characteristics of participants according to sex and K10 score at baseline (n=60 404; 2006–2010)*

Variable	All	Men	Women	K10 score at baseline†		p Value‡
				<22	≥22	
Sample size	60 404	28 057	32 347	51 393	3030	
Mean (SD) follow-up time (years)	2.67 (0.93)	2.67 (0.93)	2.68 (0.94)	2.67 (0.94)	2.72 (0.95)	0.009
Women (%)	53.6	–	–	53.3	56.2	<0.001
Mean (SD) age (years)	62.2 (10.6)	63.9 (10.7)	60.8 (10.2)§	61.6 (10.3)	58.6 (9.6)	<0.001
Highest education§ (%)						<0.001
University and higher	26.2	28.0	24.7	28.3	20.0	
High school/trade apprenticeship/certificate/Diploma	42.7	48.5	37.7	43.3	41.3	
≤10 years	31.1	23.4	37.6	28.4	68.1	
Married/living with a partner (%)	78.0	83.5	73.2§	79.6	68.1	<0.001
Household annual income§ (%)						<0.001
<$30 000	29.5	28.5	30.4	26.7	43.4	
$30 000–$69 999	28.9	31.0	27.0	29.8	25.4	
≥$70 000	25.7	29.3	22.6	28.1	16.7	
Did not specify	15.9	11.2	20.0	15.4	14.4	
BMI category§ (%)						<0.001
Underweight (<18.5 kg/m^2)	1.2	0.7	1.7	1.1	2.2	
Normal weight (18.5 to <25kg/m^2)	37.9	31.8	43.3	38.4	31.0	
Overweight or obese (≥25 kg/m^2)	60.9	67.6	55.0	60.5	66.8	
Current smoker (%)	5.7	5.7	5.7	5.3	13.9	<0.001
Usually consumes >14 alcohol drinks/week	14.9	24.7	6.3§	15.3	14.8	0.44
Mean (SD) fruit consumption (serves/day)	2.0 (1.4)	1.9 (1.5)	2.2 (1.4)§	2.0 (1.4)	1.9 (1.5)	<0.001
Mean (SD) vegetable consumption (serves/day)	3.9 (2.6)	3.4 (2.6)	4.4 (2.6)§	3.9 (2.6)	3.7 (2.7)	<0.001
Physical activity level (%)						<0.001
<150 min/week	18.9	19.2	18.8	17.5	28.0	
150–299 min/week	16.6	16.4	16.9	16.6	18.7	
≥300 min/week	64.4	64.5	64.4	65.9	53.4	
History of chronic disease (%)	51.8	56.5	47.8§	50.9	54.0	<0.001

*Data are presented as means (SD) or percentages (%).
†The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the past 4 weeks.[24] Participants were grouped according to K10 scores and categorised as at 'low-to-moderate risk' (K10<22) or at 'high-to-very high risk' of psychological distress (≥22). K10 data were missing for n=5981.
‡p Value from independent t-tests for continuous variables and from χ^2 tests for categorical variables.
§Significantly different from men (all p<0.001).
BMI, body mass index; K10, Kessler Psychological Distress Scale.

current smoker, lower education, lower household annual income, lower BMI, low physical activity levels and a self-reported history of chronic disease. There was a significant interaction between combined fruit and vegetable consumption and sex (p=0.049). When analyses were stratified by sex (table 3), the association between fruit and vegetable consumption, measured separately or combined, and the prevalence of psychological distress was markedly stronger in women and was significant for all consumption tertiles (p≤0.001). Among men, only those in the medium tertiles of separate fruit and vegetable consumption had significantly lower odds of psychological distress.

Incidence of psychological distress

After an average of 2.7 years of follow-up, 4.0% of those who did not report distress at baseline reported distress at follow-up. Table 4 shows the association between fruit and vegetable consumption and the incidence of high-to-very high levels of psychological distress (K10≥22). Similar to cross-sectional findings, fruit and vegetable consumption, measured separately or combined, was significantly associated with a lower incidence of psychological distress in unadjusted and minimally adjusted models. In the fully adjusted models, the medium tertiles of combined fruit and vegetable consumption, and separate vegetable consumption, remained significantly associated with reduced odds of psychological distress. The association between the medium tertile of fruit consumption and the incidence of psychological distress approached significance (p=0.07). However, the association between the highest tertile of consumption and the incidence of psychological distress did not remain significant for consumption of fruit and vegetables considered either separately or combined. Other covariates which were significantly associated with the incidence of psychological distress were being relatively younger, single/divorced/widowed/separated, a current smoker, lower education, lower household annual income, lower alcohol intake, lower BMI, low physical activity levels and a self-reported history of chronic disease. The interaction between

Table 2 Unadjusted and adjusted ORs for the baseline association between fruit and vegetable consumption and the prevalence of high-to-very high levels of psychological distress (K10*≥22 vs K10*<22; n=60 404)

	Prevalence/total number of cases	Unadjusted OR (95% CI)	p Value	Age-adjusted and sex-adjusted OR (95% CI)	p Value	Fully adjusted OR†(95% CI)	p Value
Tertiles							
Fruit‡							
0 to 1 serve/day	1394/21 767	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>1 to 2 serves/day	891/19 538	0.66 (0.60 to 0.72)	<0.001	0.65 (0.59 to 0.71)	<0.001	0.72 (0.65 to 0.80)	<0.001
>2 serves/day	753/16 254	0.71 (0.65 to 0.78)	<0.001	0.72 (0.65 to 0.79)	<0.001	0.87 (0.79 to 0.97)	0.01
Vegetables‡							
0 to 2 serves/day	1277/16 694	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>2 to 4 serves/day	919/15 560	0.73 (0.66 to 0.80)	<0.001	0.70 (0.64 to 0.77)	<0.001	0.81 (0.73 to 0.90)	<0.001
>4 serves/day	968/15 023	0.76 (0.70 to 0.84)	<0.001	0.75 (0.68 to 0.82)	<0.001	0.85 (0.76 to 0.94)	<0.001
Fruit and vegetables‡							
0 to 4 serves/day	1374/22 387	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>4 to 7 serves/day	1068/21 750	0.73 (0.67 to 0.79)	<0.001	0.70 (0.64 to 0.77)	<0.001	0.82 (0.74 to 0.90)	<0.001
>7 serves/day	702/14 974	0.71 (0.64 to 0.78)	<0.001	0.70 (0.63 to 0.77)	<0.001	0.82 (0.74 to 0.92)	0.001

*The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the past 4 weeks.[24] Possible K10 scores range from 10 to 50 with scores ≥22 indicating high-to-very-high levels of psychological distress.
†Adjusted for baseline age, sex, highest education level, marital status, household annual income, body mass index category, smoking status, alcohol intake, physical activity levels and a history of chronic disease.
‡There were missing cases for consumption of fruit (n=3037), vegetables (n=1190), and combined fruit and vegetables (n=1293).
K10, Kessler Psychological Distress Scale.

combined fruit and vegetable consumption and sex approached significance (p=0.08). When analyses were stratified by sex (table 3), the association between fruit and vegetable consumption, considered separately or combined, and the incidence of psychological distress was stronger in women and significant for all consumption tertiles except for the highest fruit (p=0.06), vegetable (p=0.17), and combined fruit and vegetable tertiles (p=0.09) in the fully adjusted models. There was no significant association between consumption of fruit and vegetables and the incidence of psychological distress in men.

DISCUSSION

In this large cohort of middle-aged and older Australian adults, consumption of fruit and vegetables was significantly associated with the prevalence of psychological distress even after accounting for sociodemographic characteristics and other lifestyle risk factors. The longitudinal associations with psychological distress were less consistent. The association between fruit and vegetable intake and the incidence of psychological distress was significant after accounting for age and sex. After adjustment for all possible confounders, while this association remained mostly significant at medium levels of intake, it did not remain significant at the highest levels of intake. When considered separately in each sex, the association of fruit and vegetable consumption with either the prevalence or incidence of psychological distress was stronger in women, with no clear associations with the incidence of psychological distress in men.

Findings in this study are generally in agreement with those from a recent meta-analysis, based on seven cross-sectional and four cohort studies, which has found separate fruit and vegetable consumption to be inversely associated with the risk of depression.[11] Although findings from individual cross-sectional and prospective studies were mixed, in subgroup analysis by study design, the meta-analysis showed significant associations in cross-sectional and prospective studies for fruit intake, and in prospective studies only for vegetable intake. In relation to combined fruit and vegetable consumption, several large cross-sectional studies have also demonstrated significant inverse associations with psychological well-being, even after accounting for multiple covariates.[12–14] A positive association between combined fruit and vegetable consumption and well-being, assessed using seven different measures of mental health, was shown in three separate data sets, which together involved 80 000 randomly selected British adults.[12] In a repeated cross-sectional study of 296 121 Canadians with five waves of a national, population-based survey, lower odds of depression and psychological distress were consistently associated with greater combined fruit and vegetable consumption.[13] Our cross-sectional findings are also in line with those from a recent population-based Swiss survey of 20 220 individuals, which found that daily

Table 3 Adjusted ORs for the prevalence and incidence of high-to-very high levels of psychological distress (K10*≥22 vs K10*<22) by baseline fruit and vegetable consumption and stratified by sex

	Cross-sectional analysis											
	Male						Female					
	Unadjusted OR (95% CI)	p Value	Age-adjusted OR (95% CI)	p Value	Fully adjusted OR† (95% CI)	p Value	Unadjusted OR (95% CI)	p Value	Age-adjusted OR (95% CI)	p Value	Fully adjusted OR† (95% CI)	p Value
Tertiles												
Fruit												
0 to 1 serve/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>1 to 2 serves/day	0.69 (0.59 to 0.79)	<0.001	0.71 (0.61 to 0.82)	<0.001	0.78 (0.67 to 0.91)	0.002	0.59 (0.52 to 0.66)	<0.001	0.61 (0.54 to 0.69)	<0.001	0.67 (0.59 to 0.77)	<0.001
>2 serves/day	0.80 (0.69 to 0.93)	0.003	0.83 (0.72 to 0.96)	0.02	0.99 (0.84 to 1.17)	0.95	0.61 (0.54 to 0.68)	<0.001	0.65 (0.57 to 0.73)	<0.001	0.79 (0.69 to 0.91)	0.001
Vegetables												
0 to 2 serves/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>2 to 4 serves/day	0.70 (0.61 to 0.80)	<0.001	0.71 (0.62 to 0.82)	<0.001	0.80 (0.69 to 0.93)	0.004	0.66 (0.59 to 0.75)	<0.001	0.68 (0.60 to 0.77)	<0.001	0.80 (0.70 to 0.92)	0.001
>4 serves/day	0.82 (0.71 to 0.95)	0.007	0.88 (0.76 to 1.01)	0.07	0.91 (0.78 to 1.06)	0.23	0.64 (0.57 to 0.72)	<0.001	0.68 (0.60 to 0.77)	<0.001	0.80 (0.70 to 0.92)	0.001
Fruit and vegetables												
0 to 4 serves/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>4 to 7 serves/day	0.80 (0.70 to 0.91)	0.001	0.82 (0.72 to 0.94)	0.003	0.92 (0.80 to 1.07)	0.28	0.60 (0.53 to 0.67)	<0.001	0.62 (0.55 to 0.70)	<0.001	0.73 (0.64 to 0.83)	<0.001
>7 serves/day	0.79 (0.67 to 0.93)	0.004	0.84 (0.72 to 0.99)	0.04	0.91 (0.76 to 1.09)	0.30	0.57 (0.50 to 0.65)	<0.001	0.61 (0.54 to 0.70)	<0.001	0.75 (0.65 to 0.87)	<0.001
	Longitudinal analysis‡											
	Male						**Female**					
	Unadjusted OR (95% CI)	**p Value**	**Age-adjusted OR (95% CI)**	**p Value**	**Fully adjusted OR† (95% CI)**	**p Value**	**Unadjusted OR (95% CI)**	**p Value**	**Age-adjusted OR (95% CI)**	**p Value**	**Fully adjusted OR† (95% CI)**	**p Value**
Tertiles												
Fruit												
0 to 1 serve/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>1 to 2 serves/day	0.87 (0.74 to 1.02)	0.09	0.87 (0.74 to 1.02)	0.09	0.95 (0.80 to 1.13)	0.56	0.72 (0.62 to 0.83)	<0.001	0.72 (0.62 to 0.84)	<0.001	0.84 (0.71 to 1.0)	0.04
>2 serves/day	0.90 (0.75 to 1.06)	0.21	0.89 (0.75 to, 1.06)	0.20	0.98 (0.81 to 1.19)	0.85	0.68 (0.58 to 0.80)	<0.001	0.69 (0.59 to 0.81)	<0.001	0.84 (0.70 to 1.0)	0.06
Vegetables												
0 to 2 serves/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>2 to 4 serves/day	0.86 (0.73 to 1.0)	0.05	0.85 (0.73 to 1.0)	0.05	0.94 (0.79 to 1.11)	0.45	0.67 (0.57 to 0.78)	<0.001	0.67 (0.57 to 0.78)	<0.001	0.82 (0.69 to 0.98)	0.03
>4 serves/day	0.96 (0.81 to 1.13)	0.59	0.95 (0.81 to 1.12)	0.55	0.94 (0.78 to 1.13)	0.51	0.75 (0.65 to 0.87)	<0.001	0.76 (0.65 to 0.88)	<0.001	0.89 (0.75 to 1.05)	0.17
Fruit and vegetables												
0 to 4 serves/day	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
>4 to 7 serves/day	0.88 (0.76 to 1.03)	0.11	0.88 (0.76 to 1.03)	0.11	0.98 (0.83 to 1.16)	0.82	0.63 (0.55 to 0.73)	<0.001	0.64 (0.55 to 0.74)	<0.001	0.77 (0.65 to 0.91)	0.002
>7 serves/day	0.96 (0.80 to 1.14)	0.62	0.95 (0.79 to 1.14)	0.57	0.94 (0.77 to 1.15)	0.52	0.71 (0.61 to 0.83)	<0.001	0.72 (0.62 to 0.84)	<0.001	0.86 (0.72 to 1.02)	0.09

*The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the past 4 weeks.[24] Possible K10 scores range from 10 to 50 with scores ≥22 indicating high-to-very-high levels of psychological distress.
†Adjusted for baseline age, sex, highest education level, marital status, household annual income, body mass index category, smoking status, alcoholic intake, physical activity levels and a history of chronic disease.
§Participants who reported having been recently treated for depression/anxiety and/or taking antidepressant medication and/or with a K10 score ≥22 (n=6067) at baseline were excluded from longitudinal analyses.
K10, Kessler Psychological Distress Scale.

Table 4 Unadjusted and adjusted ORs for the incidence of high-to-very high levels of psychological distress (K10*≥22) by baseline fruit and vegetable consumption (n=54 345†)

	Incident/total number of cases	Unadjusted OR (95% CI)	p Value	Age-adjusted and sex-adjusted OR (95% CI)	p Value	Fully adjusted OR‡ (95% CI)	p Value
Tertiles							
Fruit§							
0 to 1 serve/day	666/19 333	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>1 to 2 serves/day	510/17 790	0.80 (0.72 to 0.89)	<0.001	0.79 (0.71 to 0.88)	<0.001	0.89 (0.79 to 1.01)	0.07
>2 serves/day	407/14 724	0.79 (0.70 to 0.88)	<0.001	0.78 (0.69 to 0.87)	<0.001	0.90 (0.79 to 1.03)	0.11
Vegetables§							
0 to 2 serves/day	641/18 898	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>2 to 4 serves/day	486/17 281	0.77 (0.69 to 0.86)	<0.001	0.76 (0.68 to 0.85)	<0.001	0.88 (0.78 to 0.99)	0.03
>4 serves/day	511/17 103	0.87 (0.78 to 0.97)	0.01	0.85 (0.76 to 0.95)	0.003	0.92 (0.81 to 1.04)	0.16
Fruit and vegetables§							
0 to 4 serves/day	687/19 988	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>4 to 7 serves/day	548/19 671	0.77 (0.69 to 0.85)	<0.001	0.75 (0.67 to 0.83)	<0.001	0.86 (0.77 to 0.97)	0.01
>7 serves/day	396/13 560	0.85 (0.76 to 0.95)	0.005	0.82 (0.73 to 0.93)	0.001	0.90 (0.79 to 1.03)	0.12

*The total K10 score is based on a 10-item questionnaire about anxiety and depression symptoms experienced in the past 4 weeks.[24] Possible K10 scores range from 10 to 50 with scores ≥22 indicating high-to-very-high levels of psychological distress.
†Participants who reported having been recently treated for depression/anxiety and/or taking antidepressant medication and/or with a K10*score ≥22 (n=6067) at baseline were excluded from this analysis.
‡Adjusted for baseline age, sex, highest education level, marital status, household annual income, body mass index category, smoking status, alcohol intake, physical activity levels and a history of chronic disease.
§There were missing cases for consumption of fruit (n=2498), vegetables (n=1063) and combined fruit and vegetables (n=1126).
K10, Kessler Psychological Distress Scale.

recommended intake of five servings of fruit and vegetables was associated with a lower likelihood of high and moderate psychological distress.[14]

Our longitudinal findings add to the limited evidence base for an association between fruit and vegetable consumption and the incidence of psychological distress. Although longitudinal associations with psychological distress did not remain significant at higher levels of fruit and vegetable intake, the direction of these associations was in agreement with findings from previous studies. Among the few prospective studies which have examined the relationship between fruit and vegetable intake and the incidence of depression, mostly in similar-aged samples,[15–17 28] all but one study[28] have shown significant protective effects of fruit[15 17] or both fruit and vegetables.[16] A recent study involving a nationally representative sample of 12 385 Australian adults surveyed over several years reported that combined fruit and vegetable consumption was predictive of increased happiness, life satisfaction and well-being, with improvements observed within 2 years.[29] In the case of our study, the longitudinal association between fruit and vegetable consumption and psychological distress was attenuated the most between the age-adjusted and sex-adjusted model and the fully adjusted model, suggesting confounding. This may indicate that those who consume healthy amounts of fruit and vegetables are more likely to have favourable socioeconomic status and other lifestyle risk factors (eg, physical activity), which together contributed to lower psychological distress.

This study is among the first to report associations between fruit and vegetable consumption and psychological well-being separately for men and women. Sex was a significant effect modifier of the association between fruit and vegetable consumption and psychological distress. We found that fruit and vegetables were more protective for women than men, suggesting that women may be more responsive to the effects of fruit and vegetables. It is possible that there may be a true physiological difference between men and women, although a mechanism that could explain this difference remains unclear, or perhaps women more accurately report consumption of fruit and vegetables than men. However, these preliminary findings need to be confirmed by additional studies.

Future investigations should also explore the possibility of a threshold between medium and higher consumption levels. In our study, fruit and vegetable consumption at the highest levels was not protective against psychological distress in fully adjusted models, suggesting a potential threshold effect. This was also evident in the fully adjusted models in the cross-sectional analysis in men, and the longitudinal analysis in women. The reason for this observation is unknown. It is possible that consuming more fruits and vegetables beyond the potential threshold is no longer beneficial. However, the observed pattern of association could also be a result of residual confounding. For

example, participants consuming higher amounts of fruit and vegetables may also have been consuming larger quantities of other foods which could lead to psychological distress. However, despite adjusting for BMI in our analyses, this study did not measure other potential dietary confounders. The study's findings also did not change when adjusting for BMI as a continuous variable rather than a categorical variable. Participants with very high fruit and vegetable consumption may have other unmeasured characteristics that could have offset the beneficial effects of fruit and vegetable consumption. Finally, it is important to acknowledge that fruit and vegetable consumption was based on a one-time measure only, which could not take into account long-term consumption patterns. However, as compared with baseline, we found a similar pattern of consumption at follow-up (93% of participants remained in the same consumption categories between baseline and follow-up). Some of these limitations should be addressed in future studies.

Although these remain to be elucidated, several mechanisms may underlie the relationship between high fruit and vegetable consumption and greater psychological well-being.[30] Fruit and vegetables are rich in micronutrients and phytochemicals that may help reduce oxidative stress and inflammation, processes that can have detrimental effects on mental health. For example, antioxidants such as vitamins C, E and polyphenols may help reduce oxidative stress while the mineral magnesium has been associated with lower levels of C reactive protein, a marker of low-grade inflammation.[30] Deficiencies in B vitamins such as folic acid (vitamin B_9) have been associated with depression.[31] Low levels of these vitamins can cause high homocysteine levels which in turn can impair methylation processes involved in the synthesis and metabolism of neurotransmitters that may affect mood.[32]

Strengths and limitations

This study had several strengths including a large sample size, a prospective design and the inclusion of multiple sociodemographic and lifestyle-related covariates and the use of the well-validated K10 to assess psychological distress. High K10 scores are strongly correlated with CIDI diagnoses of anxiety and depression.[24] Several study limitations should be noted. The follow-up period may have been too short to observe the full extent of long-term associations between fruit and vegetable intake and psychological distress. Although the assessment of fruit and vegetable consumption was based on short validated questions, this assessment method may be prone to reporting bias. In addition, the assessment of dietary intake was not detailed and limited to a few questions only. There may be residual confounding from unmeasured dietary confounders including total energy intake and other potential confounders such as illicit drug use, a history of mental illness and unmeasured cardiometabolic components, despite adjustment for multiple covariates. Although data were available for fish consumption, another potential dietary confounder, this variable was not included as a covariate due to the lack of variance observed ('yes/no' question for ever consumption of fish only) and adjusting for fish consumption in our analyses also did not change our results. Further, the possibility of reverse causation (ie, that depression leads to poor diet including inadequate fruit and vegetable consumption) could not be eliminated, but was reduced by excluding participants being treated for depression/anxiety, taking antidepressant medication or who reported high-to-very levels of psychological distress at baseline from the longitudinal analyses. Several prospective cohort studies have not found evidence for reverse causation, with diet quality related to subsequent mental health but baseline mental health not associated with subsequent diet quality.[15 17 21] However, a recent nationally representative longitudinal study of Canadians, which explicitly tested reverse causation, showed that the association between fruit and vegetable consumption, other health behaviours and depressive symptoms are complex and bi-directional and warrants further investigation.[33]

CONCLUSIONS

Fruit and vegetable consumption may help reduce the prevalence of psychological distress among middle-aged and older adults. However, the association between fruit and vegetable consumption and the incidence of psychological distress requires further investigation and possibly, a longer follow-up time. Fruit and vegetable consumption may help reduce psychological distress among middle-aged and older females in a cross-sectional context, but not potentially at the highest levels of intake in females over time. Consumption at medium levels of intake may help lower psychological distress in men in a cross-sectional context; however, longitudinal associations remain unclear. Although findings from this study lend support to existing public health guidelines which encourage fruit and vegetable consumption as part of a healthy diet and add evidence to support the benefits of fruit and vegetables for mental health, further research is clearly needed.

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The economic burden of physical inactivity: a systematic review and critical appraisal

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ABSTRACT

Objective To summarise the literature on the economic burden of physical inactivity in populations, with emphases on appraising the methodologies and providing recommendations for future studies.

Design Systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PROSPERO registration number CRD42016047705).

Data sources Electronic databases for peer-reviewed and grey literature were systematically searched, followed by reference searching and consultation with experts.

Eligibility criteria Studies that examined the economic consequences of physical inactivity in a population/population-based sample, with clearly stated methodologies and at least an abstract/summary written in English.

Results Of the 40 eligible studies, 27 focused on direct healthcare costs only, 13 also estimated indirect costs and one study additionally estimated household costs. For direct costs, 23 studies used a population attributable fraction (PAF) approach with estimated healthcare costs attributable to physical inactivity ranging from 0.3% to 4.6% of national healthcare expenditure; 17 studies used an econometric approach, which tended to yield higher estimates than those using a PAF approach. For indirect costs, 10 studies used a human capital approach, two used a friction cost approach and one used a value of a statistical life approach. Overall, estimates varied substantially, even within the same country, depending on analytical approaches, time frame and other methodological considerations.

Conclusion Estimating the economic burden of physical inactivity is an area of increasing importance that requires further development. There is a marked lack of consistency in methodological approaches and transparency of reporting. Future studies could benefit from cross-disciplinary collaborations involving economists and physical activity experts, taking a societal perspective and following best practices in conducting and reporting analysis, including accounting for potential confounding, reverse causality and comorbidity, applying discounting and sensitivity analysis, and reporting assumptions, limitations and justifications for approaches taken. We have adapted the Consolidated Health Economic Evaluation Reporting Standards checklist as a guide for future estimates of the economic burden of physical inactivity and other risk factors.

INTRODUCTION

Physical inactivity is a global pandemic. Every year, physical inactivity causes more than 5 million deaths[1] and costs billions of dollars to societies around the world.[2] To date, many countries have developed national physical activity plans; however, few have been fully implemented.[3] The substantial gap between policy and implementation may be due to a lack of resources, cross-sectoral partnership and clear strategies. Public health responses to address the pandemic of physical inactivity remain inadequate, uncoordinated and underfunded.[3]

Economic analysis is essential to bridging the policy–implementation gap, increasing political engagement and motivating actions. Around the world, governments are addressing many competing priorities with finite resources. Making an economic case for physical activity may help galvanise public support, inform decision making and prioritise funding allocation to develop and implement interventions to reduce physical inactivity in the population.[4] Estimating the economic burden of physical inactivity is a critical first step because it can provide comprehensive information regarding the burden of the pandemic and the costs of not taking action.[2] Conducting economic evaluation of interventions designed to mitigate physical inactivity is the key to identify strategies that are the best value for money to fully inform resource prioritisation.

It is important that studies adopt robust, standardised and transparent methods when assessing the economic burden of risk factors, such as physical inactivity. Methodological consistency between studies enables valid comparisons regarding the absolute and relative burden of physical inactivity compared with other risk factors. This can be expected to increase the confidence of decision makers to commission and use such analyses in decision making. To date, a range of studies have been published on the economic burden of physical inactivity at local, state or national levels, mostly in developed countries. In 2016, as part of the *Lancet* Physical Activity Series, we published the first global estimate that included 142 countries.[2] However, prior estimates, even for the same country, vary substantially across studies. For example, Carlson *et al* estimated that physical inactivity accounted for 11.1% of the healthcare expenditure in the USA[5] while Colditz estimated the proportion to be 2.4%.[6] The difference between 11.1% and 2.4% is enormous. Understanding and perhaps resolving such divergent estimates is crucially important to enhance the overall credibility of economic burden estimates in decision making.

The purpose of this paper is to undertake a systematic review of the current literature on the

economic burden of physical inactivity in populations or population-based samples, with emphases on a critical appraisal of the methodologies of each study and a discussion on how the conduct and interpretation of future studies may be improved.

METHODS

Data sources and searches

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42016047705, available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016047705). This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

We identified studies through searching electronic databases, including Medline (via OvidSP; 1946–present), Scopus and Global Health (via OvidSP; 1910–present) for peer-reviewed papers, and Web of Science conference proceedings (1900-present), ProQuest Dissertations and Theses Global, Google Scholar and Google for grey literature. The literature search was conducted from database inception to October 2016, using search terms outlined in supplementary file 1. Additional articles were identified through searching the references of eligible articles and consultation with experts in the field (authors of the global estimate paper by Ding *et al*[2] and experts listed in the Acknowledgements section of that paper).

Eligibility criteria

A study was considered eligible if it: (1) examined physical inactivity as a risk factor; (2) examined the economic burden of physical inactivity in any format, such as an estimated amount, a percentage (eg, of healthcare expenditure) or the differential costs between those who were physically inactive and those who were not; (3) provided estimates based on a population (eg, Canadian adults) or a population-based sample (eg, the Australian Longitudinal Study on Women's Health); (4) provided sufficient methodological details to allow for data extraction; and (5) included an English abstract or summary. No additional restrictions regarding the date of publication, language or peer-review status were imposed.

A study was excluded if it was based on a workplace sample only,[8] if it provided little information on methodologies or used a patented technique or tool[9] or if it included physical inactivity as a component of an overall lifestyle index or factor.[10] Finally, publications that did not include original analysis, such as reviews and commentaries, were also excluded.

Study selection

Eligibility of identified studies was assessed independently by two authors (DD and TLK-A) following a standard protocol that involved reading the title, abstract and full-text articles. Uncertainty was discussed after reading the full text, and any disagreement was resolved by consensus. A PRISMA flow diagram presents the summary of the study selection process (figure 1).

Data extraction

The outcomes of the studies included direct (ie, healthcare expenditure) and indirect costs (eg, productivity losses). Studies estimating the direct healthcare costs of physical inactivity

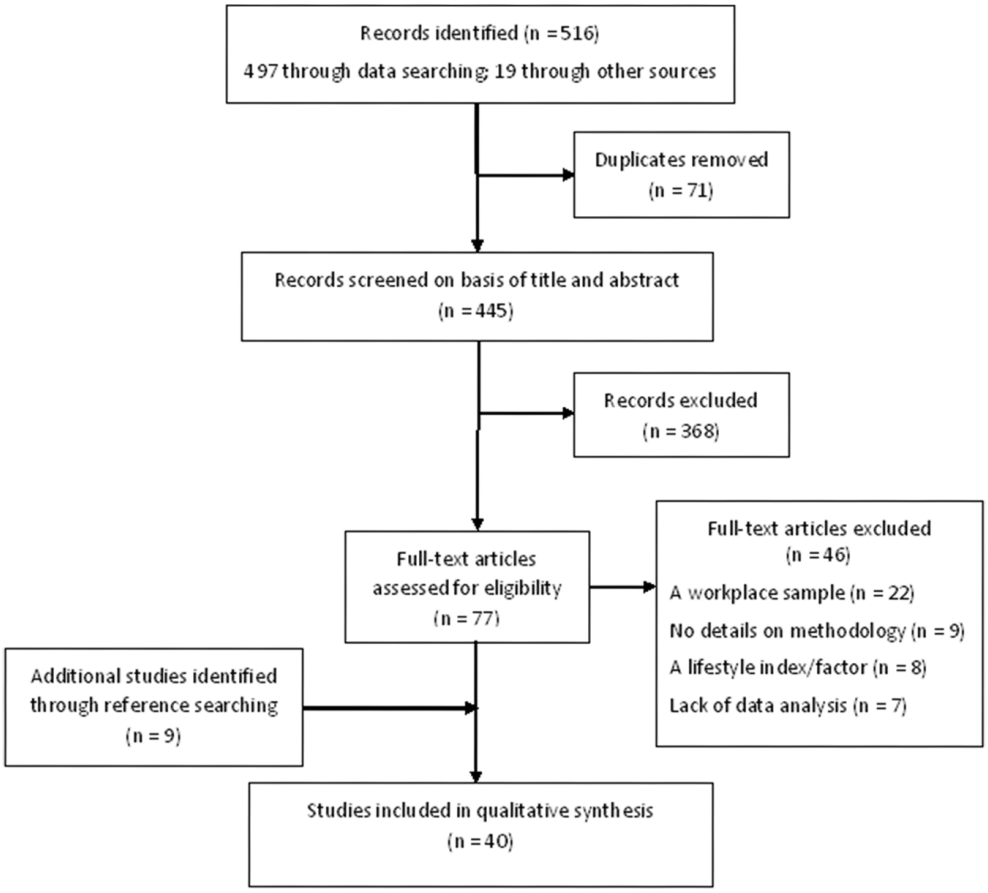

Figure 1 Selection of articles for systematic review.

Table 1 Characteristics of studies (n=40)

Study characteristic	No. of studies	References (first author and year of publication)
Country		
Australia	5	Brown 2008[43]; Cadilhac 2011[27]; Musich 2003[44]; Peeters 2014[36]; Stephenson 2000[30]
Brazil	2	Bielemann 2015[29]; Codogno 2015[48]
Canada	8	Colman 2004[16]; Janssen 2012[18]; Katzmarzyk 2000[33]; Katzmarzyk 2004[20]; Katzmarzyk 2011[19]; Krueger 2014[23]; Krueger 2015[22]; Krueger 2016[21]
China	2	Popkin 2006[57]; Zhang 2013[26]
Czech Republic	1	Maresova 2014[31]
Japan	2	Aoyagi 2011[42]; Yang 2011[37]
Korea	2	Cho 2011[39]; Min 2016[38]
New Zealand	1	Market Economics Limited 2013[24]
Switzerland	1	Martin 2001[25]
Taiwan	1	Lin 2008[45]
UK	3	Allender 2007[58]; Scarborough 2011[34]; Townsend 2016[32]
USA	10	Anderson 2005[59]; Andreyeva 2006[35]; Carlson 2014[5]; Chevan 2014[46]; Colditz 1999[6]; Garrett 2004[60]; Pratt 2000[40]; Pronk 1999[47]; Wang 2004a[41]; Wang 2004b[49]
Multiple countries	2	International Sports and Culture Association and Centre for Economics and Business Research 2015[17]; Ding 2016[2]
Study perspective		
Healthcare payer only	27	Allender 2007[58]; Anderson 2005[59]; Andreyeva 2006[35]; Aoyagi 2011[42]; Bielemann 2015[29]; Brown 2008[43]; Carlson 2014[5]; Chevan 2014[46]; Cho, 2011[39]; Codogno 2015[48]; Colditz 1999[6]; Garrett 2004[60]; Katzmarzyk 2000[33]; Lin 2008[45]; Maresova 2014[31]; Min 2016[38]; Musich 2003[44]; Peeters 2014[36]; Popkin 2006[57]; Pratt 2000[40]; Pronk 1999[47]; Scarborough 2011[34]; Stephenson 2000[30]; Townsend 2016[32]; Wang 2004a[41]; Wang 2004b[49]; Yang 2011[37]
Healthcare payer and the economy	12	Colman 2004[16]; Ding 2016[2]; International Sports and Culture Association and Centre for Economics and Business Research 2015[17]; Janssen 2012[18]; Katzmarzyk 2004[20]; Katzmarzyk 2011[19]; Krueger 2014[23]; Krueger 2015[22]; Krueger 2016[21]; Market Economics Limited 2013[24]; Martin 2001[25]; Zhang 2013[26]
Societal*	1	Cadilhac 2011[27]
Methodology for estimating direct healthcare costs		
Population attributable fraction (PAF)-based approach	23	Allender 2007[58]; Bielemann 2015[29]; Cadilhac 2011[27]; Colditz 1999[6]; Colman 2004[16]; Ding 2016[2]; Garrett 2004[60]; International Sports and Culture Association and Centre for Economics and Business Research 2015[17]; Janssen 2012[18]; Katzmarzyk 2000[33]; Katzmarzyk 2004[20]; Katzmarzyk 2011[19]; Krueger 2014[23]; Krueger 2015[22]; Krueger 2016[21]; Maresova 2014[31]; Market Economics Limited 2013[24]; Martin 2001[25]; Popkin 2006[57]; Scarborough 2011[34]; Stephenson 2000[30]; Townsend 2016[32]; Zhang 2013[26]
Econometric approach	17	Anderson 2005[59]; Andreyeva 2006[35]; Aoyagi 2011[42]; Brown 2008[43]; Carlson 2014[5]; Chevan 2014[46]; Cho 2011[39]; Codogno 2015[48]; Lin 2008[45]; Min 2016[38]; Musich 2003[44]; Peeters 2014[36]; Pratt 2000[40]; Pronk 1999[47]; Wang 2004a[41]; Wang 2004b[49]; Yang 2011[37]
Indirect costs estimated		
Yes	13	Cadilhac 2011[27]; Colman 2004[16]; Ding 2016[2]; International Sports and Culture Association and Centre for Economics and Business Research 2015[17]; Janssen 2012[18]; Katzmarzyk 2004[20]; Katzmarzyk 2011[19]; Krueger 2014[23]; Krueger 2015[22]; Krueger 2016[21]; Market Economics Limited 2013[24]; Martin 2001[25]; Zhang 2013[26]
No	27	Allender 2007[58]; Anderson 2005[59]; Andreyeva 2006[35]; Aoyagi 2011[42]; Bielemann 2015[29]; Brown 2008[43]; Carlson 2014[5]; Chevan 2014[46]; Cho 2011[39]; Codogno 2015[48]; Colditz 1999[6]; Garrett 2004[60]; Katzmarzyk 2000[33]; Lin 2008[45]; Maresova 2014[31]; Min 2016[38]; Musich 2003[44]; Peeters 2014[36]; Popkin 2006[57]; Pratt 2000[40]; Pronk 1999[47]; Scarborough 2011[34]; Stephenson 2000[30]; Townsend 2016[32]; Wang 2004a[41]; Wang 2004b[49]; Yang 2011[37]
Type of publication		
Peer-reviewed scientific paper	35	Allender 2007[58]; Anderson 2005[59]; Andreyeva 2006[35]; Aoyagi 2011[42]; Bielemann 2015[29]; Brown 2008[43]; Cadilhac 2011[27]; Carlson 2014[5]; Chevan 2014[46]; Cho 2011[39]; Codogno 2015[48]; Colditz 1999[6]; Ding 2016[2]; Garrett 2004[60]; Janssen 2012[18]; Katzmarzyk 2000[33]; Katzmarzyk 2004[20]; Katzmarzyk 2011[19]; Krueger 2014[23]; Krueger 2015[22]; Krueger 2016[21]; Lin 2008[45]; Maresova 2014[31]; Martin 2001[25]; Min 2016[38]; Musich 2003[44]; Peeters 2014[36]; Popkin 2006[57]; Pratt 2000[40]; Pronk 1999[47]; Scarborough 2011[34]; Wang 2004a[41]; Wang 2004b[49]; Yang 2011[37]; Zhang 2013[26]
Grey literature	5	Colman 2004[16]; International Sports and Culture Association and Centre for Economics and Business Research 2015[17]; Market Economics Limited 2013[24]; Stephenson 2000[30]; Townsend 2016[32]

*Combined perspectives from the healthcare payer, the economy and the household.
References of all studies are included in online supplementary file 2.

generally used two approaches: (1) a PAF-based approach, which calculates healthcare costs attributable to physical inactivity by applying a PAF (interpreted as the proportion of disease that would not exist if physical inactivity was eliminated) to disease-specific costs; and (2) an econometric approach, which uses data linking physical inactivity and healthcare expenditure at the individual level. Data were extracted separately for direct and indirect costs and for studies that used a PAF-based and an econometric approach.

One author (DD) extracted data from studies, and two other authors (TLK-A, BN) each independently re-entered 30% of the extracted data for quality assurance. Any disagreement was resolved by consensus. Extracted data elements included country, data sources, physical activity measures (eg, minimal risk counterfactual or physical activity categories), time frame (eg, 1 year vs lifetime) and perspective of the analysis (eg, 'healthcare payer', 'household', 'economy' or 'societal').[11] Various other methodological considerations were extracted. Specifically, for

studies that estimated direct healthcare costs using a PAF-based approach, we extracted data on the diseases or health conditions included in the cost estimates (eg, diabetes and stroke), whether the PAF was based on crude or adjusted relative risks (RRs) and whether comorbidity among diseases was accounted for. For studies using an econometric approach, we extracted data on the study design (eg, longitudinal and cross-sectional), sample, the types of costs included (eg, inpatient and outpatient) and adjustment for covariates. Finally, we also extracted information on the reported funding sources and conflict of interest.

For studies that estimated indirect costs, we extracted the type of costs included (eg, productivity losses from absenteeism, presentism and others) and the methodology used. Three main approaches were used. The friction cost approach (FCA) takes an 'employer perspective' to estimate productivity losses during the 'friction period', which is the time before an employer replaces the worker lost to death or disability.[12] The human capital approach (HCA) takes an 'employee perspective' and estimates the productivity losses over an expected working lifetime, irrespective of whether an individual dies from the risk factor and/or an employer can replace the worker.[13] Finally, a value of a statistical life (VSL) approach monetises an average or 'statistical' life lost.[14] The key difference of a VSL approach is that it seeks to value life lost as opposed to estimating the productivity costs incurred. Overall, the estimates produced differ across methods, increasing from FCA to HCA to VSL.

For studies that involved an estimate of the economic burden over time, we extracted information on whether discounting was applied. Discounting is a process where all present and future costs are converted to a single net present value (NPV). Discounting is an essential practice in robust economic analysis.[15]

Finally, we extracted information on any uncertainty analysis/sensitivity analysis regarding the estimates produced. We searched for whether studies investigated statistical uncertainty and/or structural uncertainty. Statistical uncertainty concerns input parameters to the model and corresponding estimates of the economic burden the model produced. Statistical uncertainty is typically represented by means and standard errors/confidence intervals, and statistical sensitivity analysis explores sampling from the distributions to understand how the economic burden varies. Possibilities include, for example, multiway sensitivity analysis and probability sensitivity analysis. Structural uncertainty concerns the nature of the model (eg, uncertainty in the econometric assumptions used) and/or parameters included (eg, using FCA, HCA or VSL when estimating indirect costs). Structural sensitivity analysis explicitly investigates such uncertainties if relevant, by varying the model as appropriate (eg, different parameters and functional forms) and reporting the corresponding change in the economic burden estimates produced.

In the case of lacking specific information (eg, types of cost included), we examined the references provided by the authors to obtain relevant information. If the information was not available, we coded it as 'not specified', and when the information provided was ambiguous, we coded it as 'unclear'.

Risk of bias assessment

Due to the lack of risk of bias assessment tools or established methodological guidance on how to conduct a high-quality analysis of the economic burden of physical inactivity (or other lifestyle risk factor), we did not perform a formal risk of bias assessment according to an existing instrument, nor did we exclude studies based on low quality. Instead, we extensively discussed methodological and presentation issues throughout the paper and developed a checklist that could be used for future original studies and quality assessment.

Data synthesis

General characteristics of the selected studies, including country, perspective, methodology for estimating direct healthcare costs, whether indirect costs were estimated and type of publication, were summarised in a table. Additional specific information extracted from each study (see 'Data extraction') was synthesised separately by the type of costs (direct vs indirect costs) and the methodological approaches to estimating direct healthcare costs (PAF-based vs econometric).

To facilitate comparison of estimates across studies, we presented the percentage of overall healthcare expenditure attributable to physical inactivity. When the percentage was not reported by the study but the overall physical inactivity-related healthcare expenditure was available, we calculated the percentage based on the overall healthcare expenditure data for that year from the WHO website (http://apps.who.int/nha/database/Select/Indicators/en). Additionally, to facilitate comparison of national estimates from different years and in different currencies, we inflated the national estimates (point estimates only) in local currency units from the year of data to 2013, as the common year, using the annual consumer prices inflation indicators from the World Bank (http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG) and then converted to purchasing power parity (PPP) international dollars using conversion factors provided by the World Bank (http://data.worldbank.org/indicator/PA.NUS.PPP). This approach, similar to that used in our recent global estimates,[2] allows for comparison across countries using a common currency taking PPP into account. Finally, when the authors presented incorrect information (eg, using incorrect exchange rate and inappropriately calculated healthcare expenditure percentages), we attempted to present corrected information in summary tables and noted the correction in footnotes.

RESULTS

Selection of studies

As shown in figure 1, a total of 516 studies were identified, of which 445 were unique records. After excluding 368 records based on reading the title and abstract, full texts of the remaining 77 studies were examined. A total of 46 studies were excluded because they did not meet the inclusion criteria. In total, 40 studies were qualitatively synthesised and appraised (see online supplementary file 2).

Study characteristics

Table 1 demonstrates characteristics of the 40 studies. Nearly half of the identified studies were conducted in North America (10 in the US and eight in Canada), five studies were conducted in Australia, three in the UK, two were across multiple countries and the rest of the studies were conducted in Brazil, China, Czech Republic, Japan, Korea, Switzerland, New Zealand and Taiwan. Overall, 35 studies were peer-reviewed and five were grey literature reports.

Perspective

Two-thirds of the studies (n=27) took the sole perspective of the healthcare payer and estimated the direct healthcare expenditure only. Of the 13 studies that also estimated the indirect costs of physical inactivity, 12 combined the perspectives of the healthcare payer and the economy, by additionally estimating costs of

productivity losses.[2 16–26] Only one study took a comprehensive societal perspective by estimating direct healthcare costs, indirect costs of productivity losses and those of home-based and leisure-based production.[27]

Estimates of direct costs

All studies included some estimates of the direct heathcare costs of physical inactivity. Of those, 23 studies used a PAF-based approach, while 17 used an econometric approach.

Converted national estimate: we inflated the national estimates in local currency units from the year of data to 2013 using the annual consumer prices inflation indicators from the World Bank (http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG) and then converted to PPP international dollars using conversion factors provided by the World Bank (http://data.worldbank.org/indicator/PA.NUS.PPP). However, the estimate was not converted for Martin *et al*[25] due to the lack of Swiss franc (SFr) to PPP international dollar conversion factor from the World Bank.

Studies using a PAF-based approach

As shown in table 2, although the 23 studies did not use a standardised minimal risk counterfactual for calculating the PAF, most used a definition that was equivalent to approximately 150 min of moderate-intensity physical activity per week as recommended by current physical activity guidelines.[28] Almost all studies included a broad range of healthcare expenditure, such as inpatient, outpatient, pharmaceutical and physician care costs. One study included inpatient costs only.[29] In estimating direct healthcare costs, studies included between four and eight health conditions, nearly all of which included ischaemic heart disease, diabetes, breast cancer and colon cancer. Some studies included additional conditions, such as stroke, hypertension and osteoporosis.

Regarding the PAF used for estimating direct healthcare costs, most studies did not specify whether the PAF was based on adjusted or unadjusted RR. After checking the cited references about the PAF, we could only confirm that nine studies used PAF based on adjusted RR.[2 18 19 21–23 26 29 30] All studies took an additive approach by summing costs attributable to physical inactivity across multiple diseases/conditions. This could potentially lead to double counting among those with multiple conditions, commonly known as comorbidity. Only two studies explicitly described efforts to address comorbidity. One study estimated the potential overlaps among ischaemic heart disease, stroke, and type 2 diabetes and subtracted the overlapped proportions from the sum.[2] The other study used data that could identify comorbidity through individual hospital records.[24]

All studies provided an overall amount for the healthcare costs of physical inactivity for a one-year time frame. Nineteen of the 23 studies provided a national level estimate, most of which was presented as or converted to a percentage of national healthcare expenditure. The percentages ranged from around 0.3% in the Czech Republic[31] and England[32] to 4.6% in New Zealand,[24] with the majority of the estimates ranging between 1% and 2.5% (Supplementary Figure 1). Twelve studies provided some sensitivity analysis.[2 6 18 20–25 30 33 34] Of those, four included structural sensitivity analysis, by taking into account different physical activity prevalence and/or PAF.[2 25 30 34]

Studies using an econometric approach

Of the 17 studies that used an econometric approach, three applied a longitudinal design,[35–37] one used a retrospective cohort design,[38] and the remainder were cross-sectional studies (table 3). The sample size of studies ranged from 250 to 51 165. The measurement and categorisation of physical activity varied across studies and often included multiple levels. In most cases, healthcare cost data were measured objectively, based on health insurance claims or data from other healthcare systems. Only three studies used self-reported health expenditure data.[39–41] In most cases, health cost data included comprehensive types of expenditure, including both inpatient and outpatient care. However, two studies did not include inpatient services,[42 43] and one study primarily included inpatient services.[44] The types of expenditure included in each study depended on the data sources, such as public systems versus private health insurance companies.

Findings from these studies were presented in heterogeneous formats. For example, some studies presented excessive healthcare costs among those who were less active (or cost savings among those who were active), in terms of absolute or proportional difference,[5 38–40 43–45] some presented the magnitude of association between physical activity and healthcare expenditure[42 46 47] and a number of studies extrapolated findings from the sample to the population at the national level.[5 35 36 40 41 43 48 49] Overall, based on the converted national-level estimates of the proportion of healthcare expenditure associated with physical inactivity, studies that applied an econometric approach produced much higher estimates than those applying a PAF-based approach (Supplementary Figure 1). Only two econometric studies included structural sensitivity analyses by taking into account alternative model forms.[5 35]

Estimates of indirect costs

All of the 13 studies provided estimates of productivity losses in the workforce (table 4). Of those, the majority of the studies applied HCA and estimated cumulative productivity losses over a working lifetime of population affected (including current and future costs).[16–23 25 26] Two studies used FCA to estimate productivity losses during the replacement period.[2 27] In studies where both HCA and FCA were used, in the form of sensitivity analysis, FCA yielded much lower costs than HCA.[2 22 27] One study used a VSL approach and had much higher estimates of indirect costs than studies applying HCA and FCA.[24] Although at least 10 studies provided lifetime estimates by incorporating costs that will occur in the future, only four explicitly described discounting future costs,[18 20 24 27] another five were identified as applying discounting on checking their references or data sources.[16 19 21–23] Most studies included some form of statistical sensitivity analysis.[2 18 20–25 27] Five studies conducted structural sensitivity analysis by varying the model using alternative approaches/parameters.[2 22 24 25 27]

DISCUSSION

To our knowledge, the current systematic review is the first to comprehensively summarise findings and methodological considerations of studies estimating the economic burden of physical inactivity in populations. Although 40 studies were included in our review, the current estimates stem disproportionately from a small number of countries. Specifically, 38 single-country studies represented only 12 countries, of which 10 were high-income countries. At the global level, estimating the economic burden of physical inactivity remains an important yet underdeveloped area, particularly in low-income and middle-income countries.[4]

Based on the findings from the studies reviewed, it is evident that physical inactivity is a costly pandemic that is associated

Table 2 Characteristics of studies that applied a population attributable fraction (PAF) approach to estimating direct healthcare costs of physical inactivity (n=23)

First author and year of publication	Country	Data sources	Definition of PA minimal risk counterfactual	Types of costs	Conditions included	Adjusted PAF*	Comorbidity†	Findings‡: amount (% healthcare cost), uncertainty/sensitivity analysis	Time frame	Funding/COI
Peer-reviewed scientific paper										
Allender 2007[58]	UK	NHS 2002 total expenditure data, NHS 1992–1993 expenditure by disease code data	2.5 hours MPA or 1 hour VPA/week	Inpatient, outpatient, primary and community care, pharmaceutical	IHD, stroke, breast cancer, colon cancer, diabetes	No/unclear	No	£1.06 billion (1.5%) Converted national estimate: $2.0 billion INT	1 year (2002)	British Heart Foundation/no COI declared
Bielemann 2015[29]	Brazil	Brazilian Unified Health System data 2013, Brazil National Household Sample Survey 2008	Any leisure time PA	Inpatient costs only	IHD, stroke, hypertension, breast cancer, colon cancer, diabetes, osteoporosis	Yes	No	R$141.9 million, 15% of total inpatient costs of the seven major NCDs Converted national estimate: $86.2 million INT	1 year (2013)	No funding reported/ no COI declared
Cadilhac 2011[27]	Australia	National Health Survey 2004–2005, Australian Burden of Disease data 2003, Disease Costs and Impact Study 2000–2001	≥5×30 min MPA or ≥3×20 min VPA/week	Annual health sector cost	IHD, stroke, cancers, fractures, depression	No/unclear	No	$A672 million (1.3%) Converted national estimate: $522.7 million INT	1 year (2008)	VicHealth/no COI declared
Colditz 1999[6]	USA	Previously published cost estimates for each disease	Any leisure time PA	Hospital care, pharmaceutical, physician care, care in nursing home	IHD, hypertension, breast cancer, colon cancer, diabetes, osteoporotic fractures	No/unclear	No	US$24.3 billion (2.4%), statistical sensitivity analysis: US$37.2 billion (3.7%) Converted national estimate: $37.2 billion INT	1 year (1995)	Boston Obesity Nutrition Research Centre/COI statement missing
Ding 2016[2]	142 countries	WHO, World Bank and GBD Study data	≥150 min MVPA/week	Total health expenditure	IHD, stroke, breast cancer, colon cancer, T2DM	Yes	Yes	$53.8 billion INT worldwide (0.64%), structural and statistical sensitivity analysis: $14.9–147.6 billion INT when using unadjusted PAFs: $123.9 ($40.9–291.2) billion INT	1 year (2013)	No funding reported/ no COI declared
Garrett 2004[60]	USA	Blue Cross databases and Behavioral Risk Factor Surveillance System	≥5×30 min MPA or ≥3×20 min VPA/week	Inpatient and outpatient medical claim	IHD, stroke, hypertension, breast cancer, colon cancer, T2DM, osteoporotic fractures, depression, anxiety	No/unclear	No	US$83.6 million ($56/ member) among US Blue Cross members	1 year (2000)	No funding reported/ Blue Cross and Blue Shield employees involved as authors
Janssen 2012[18]	Canada	Canadian Health Measures Survey 2007–2009, EBIC 2000	7-day accelerometry ≥150 min/week	Hospital care, pharmaceutical, physician care, care in other institution and additional care expenditure	IHD, stroke, hypertension, breast cancer, colon cancer, T2DM, osteoporosis	Yes	No	$C2.4 billion (1.4%§), statistical sensitivity analysis: $C1.6–3.1 billion Converted national estimate: $2.1 billion INT	1 year (2009)	Public Health Agency of Canada/COI statement missing

Continued

Table 2 Continued

First author and year of publication	Country	Data sources	Definition of PA minimal risk counterfactual	Types of costs	Conditions included	Adjusted PAF*	Comorbidity†	Findings‡: amount (% healthcare cost), uncertainty/sensitivity analysis	Time frame	Funding/COI
Katzmarzyk 2000[33]	Canada	EBIC 1993, the PA Monitor Survey	Energy expenditure ≥12.6 kJ/kg/day	Hospital care, pharmaceutical, physician care and research	IHD, stroke, hypertension, breast cancer, colon cancer, T2DM, osteoporosis	No/unclear	No	$C2.1 billion (2.5%), statistical sensitivity analysis: $C1.4–3.1 billion Converted national estimate: $2.3 billion INT	1 year (1999)	Canadian Society for Exercise Physiology and Health Canada/no COI declared
Katzmarzyk 2004[20]	Canada	CCHS 2000–2001, EBIC 1998/1993	Expenditure ≥6.3 kJ/kg/day	Hospital care, pharmaceutical, physician care, care in other institution and additional care expenditure	IHD, stroke, hypertension, breast cancer, colon cancer, T2DM, osteoporosis	No/unclear	No	$C1.6 billion (1.5%), statistical sensitivity analysis conducted for total costs Converted national estimate: $1.7 billion INT	1 year (2001)	Ontario Ministry of Tourism and Recreation/COI statement missing
Katzmarzyk 2011[19]	Canada	CCHS 2009, EBIC 1998	Expenditure ≥6.3 kJ/kg/day	Hospital care, pharmaceutical, physician care, care in other institution and additional care expenditure	Coronary artery disease, stroke, hypertension, colon cancer, breast cancer, T2DM, osteoporosis	Yes	No	$C1.02 billion in Ontario, Canada	1 year (2009)	Ontario Ministry of Health Promotion/COI statement missing
Krueger 2014[23]	Canada	NHEX, CCHS 2009, EBIC 1998, Canadian Institute for Health Information Hospital Morbidity Database	Not defined as 'inactive' (did not specify)	Hospital care, pharmaceutical, physician care, other healthcare professionals (excluding dental), health research and other	IHD, stroke, hypertension, breast cancer, colon cancer, T2DM, osteoporosis	Yes	No	$C3 billion (1.4%), statistical sensitivity analysis conducted for combined risk factors Converted national estimate: $2.5 billion INT	1 year (2012)	No funding reported/ no COI declared
Krueger 2015[22]	Canada	NHEX, CCHS 2012, EBIC 2008	Leisure time energy expenditure ≥1.5 kcal/ kg/day	Same as above	Same as above	Yes	No	$C3.27 billion (1.6%¶), quoted previous statistical sensitivity analysis ±17% Converted national estimate: $2.7 billion INT	1 year (2013)	No funding reported/ no COI declared
Krueger 2016[21]	Canada	NHEX, CCHS 2011–2012, EBIC 2008	Leisure time energy expenditure ≥1.5 kcal/ kg/day	Same as above	Same as above	Yes	No	$C349.6 million for British Columbia, Canada, quoted previous statistical sensitivity analysis ±17%	1 year (2013)	Ministry of Health and Provincial Health Services Authority/COI statement missing

Continued

Table 2 Continued

First author and year of publication	Country	Data sources	Definition of PA minimal risk counterfactual	Types of costs	Conditions included	Adjusted PAF*	Comorbidity†	Findings‡: amount (% healthcare cost), uncertainty/sensitivity analysis	Time frame	Funding/COI
Maresova 2014[31]	Czech Republic	Czech Republic European Health Interview Survey 2008, WHO GBD Study, data from health insurance companies that cover 75% of all healthcare expenditures	≥150 min/week MPA, ≥75 min/week VPA, or ≥180 min/week walking, or any combination resulting in 600 MET min over at least 3 days/week	Not specified	IHD, ischaemic stroke, breast cancer, colon cancer, T2DM	No/unclear	No	693 million CZK (0.35%) Converted national estimate: $58.8 million INT	1 year (2008)	University of Economics, Prague/ COI statement missing
Martin 2001[25]	Switzerland	Health-enhancing PA survey 1999, a published study on costs associated with each disease, accident statistics from the Swiss Council for Accident Prevention	≥5×30 min MPA or ≥3×20 min VPA	Not specified	CVD, hypertension, breast cancer, colon cancer, T2DM, osteoporosis, back pain, depression	No/unclear	No	2.7 billion SFr (structural sensitivity analysis conducted)	Not specified	No funding reported/ COI statement missing
Popkin 2006[57]	China	China Health and Nutrition Survey 2000, National Health Services Survey 1998	Not specified	Total costs: inpatient, outpatient, pharmaceutical, and other.	IHD, stroke hypertension, breast cancer, colon cancer, endometrial cancer, T2DM (also included costs of NCDs indirectly through overweight/ obesity)	No/unclear	No	US$1.35 billion (2.4%¶) Converted national estimate: $4.3 billion INT	1 year (2000; projected 2025 cost provided)	No funding reported/ no COI declared
Scarborough 2011[34]	UK	NHS Programme Budgeting estimates, WHO GBD Project	Achieving some PA at work, home, for transport or during discretionary time	All spending in primary and secondary care services	IHD, stroke, breast cancer, colon cancer, diabetes	No/unclear	No	£0.9 billion (0.75%¶), structural sensitivity analysis: £0.9–1.0 billion Converted national estimate: $1.6 billion INT	1 year (2006–07)	British Heart Foundation/COI statement missing
Zhang 2013[26]	China	Chinese Behavioral Risk Factors Surveillance 2007, National Health Services Survey 2003	≥5×30 min MPA or ≥3×20 min VPA/week	Hospital care, pharmaceutical, physician care and additional health expenditures	IHD, stroke, hypertension, cancer, T2DM (also included costs of NCDs indirectly through overweight/ obesity)	Yes	No	US$3.5 billion (2.4%¶) Converted national estimate: $9.1 billion INT	1 year (2007)	Nike Inc./no COI declared
Grey literature										
Colman 2004[16]	Canada	CCHS 2000–2001, EBIC 1998	Expenditure ≥1.5 kcal/ kg/day	Hospital care, pharmaceutical, physician care, other institutions (including research), additional drug expenditure, private spending on medical care	CVD, cancer, endocrine and related diseases, musculoskeletal diseases	No/unclear	No	$C210.8 million for British Columbia, Canada.	1 year (2001)	B.C. Ministry of Health Planning/COI statement missing

Continued

Table 2 Continued

First author and year of publication	Country	Data sources	Definition of PA minimal risk counterfactual	Types of costs	Conditions included	Adjusted PAF*	Comorbidity†	Findings‡: amount (% healthcare cost), uncertainty/sensitivity analysis	Time frame	Funding/COI
International Sports and Culture Association and Centre for Economics and Business Research 2015[17]	EU-28	WHO, Organization for Economic Cooperation and Development, Eurostat, International Development Association, EUCAN and published studies	≥150 min MPA or ≥75 min VPA/week, or combinations	Direct costs: healthcare expenditure Indirect costs: DALYs	IHD, breast cancer, colorectal cancer, T2DM	No/unclear	No	UK: €1920 million (1.06%§); Germany: €1677 million (0.55%§); Italy: €1562 million (1.04%§); France: €1215 million (0.51%§); Spain: €992 million (1.03%§); Poland: €219 million (0.86%§). EU-28: €9.2 billion Converted national estimates: UK $2.4; Germany $2.2; Italy $2.1; France $1.5; Spain $1.5; Poland $0.5 billion INT	1 year (2012)	International Sport and Culture Association (contributors included various organisations and companies)/COI statement missing
Market Economics Limited 2013[24]	New Zealand	Various sources including the Ministry of Health, Statistics New Zealand, District Health Board reports, and others	≥30 min PA×5 days/week	Hospital care, pharmaceutical, outpatient, public health and other	IHD, stroke, hypertension, breast cancer, colorectal cancer, T2DM, osteoporosis, depression	No/unclear	Yes	$614 million NZD (4.6%), statistical sensitivity analysis conducted (+2%) Converted national estimate: $464.4 million INT	2010	Government commissioned/COI statement missing
Stephenson 2000[30]	Australia	Active Australia 1997 National PA Survey; RR from studies on PA and disease; Australian Institute of Health and Welfare's Disease Costs and Impact Study	Inactivity ≥150 min/week	Hospital care, pharmaceutical, medical services, allied health, research, public health and other	IHD, stroke, breast cancer, colon cancer, depression	Yes	No	$A377 million (1.1%#; structural sensitivity analysis conducted) Converted national estimate: $433.2 million INT	1 year (1993–1994)	Commonwealth Department of Health and Aged Care and Australian Sports Commission/COI statement missing
Public Health England 2016	UK	Programme budgeting data released by NHS England in 2010–2014	Not specified	Not specified	IHD, stroke, breast cancer, colon cancer, diabetes	No/unclear	No	£455 million for England, UK (0.3%#) Converted national estimate: $657.8 million INT	1 year (2013–2014)	Public Health England/COI statement missing

*Adjusted PAF: whether PAF used was based on relative risks adjusted for confounders. Yes=explicitly described adjustment in the paper; No/unclear=did not describe adjustment in the paper, we could not use a consistent methodology to determine whether the PAF was crude or adjusted but not stated.
†Comorbidity: whether the potential double counting among comorbidities was addressed (yes/no).
‡Findings: interpreted as the total amount of direct healthcare cost that was associated with physical inactivity (all findings referred to the general population with the exception of Garrett 2004,[60] which referred to all Blue Cross members ≥18 years). % interpreted as the percentage of overall healthcare cost that was spent on diseases that were attributable to physical inactivity. In most cases, the percentages were reported in the original studies; in some cases, the author (DD) calculated or recalculated the percentages based on national healthcare expenditure data from the WHO (available at http://apps.who.int/nha/database/ViewData/Indicators/en).
§Recalculated and corrected by the authors of the current review.
¶Calculated or recalculated percentages.
A, Australian dollars; C, Canadian dollars; CCHS, Canadian Community Health Survey; COI, conflict of interest; CVD, cardiovascular disease; CZK, Czech Koruna; DALYs, Disability Adjusted Life Years; EBIC, Economic Burden of Illness in Canada; EU-28, 28 member countries of the European Union; GBD: Global Burden of Disease; IHD, ischaemic heart disease; INT, international dollars; MET, metabolic equivalents; min, minutes; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; NCD, non-communicable disease; NHEX, National Health Expenditure Database for Canada; NHS, National Health Service; NZD, New Zealand dollars; min, minutes; PA, physical activity; PAF, population attributable fraction; £, pounds sterling; R, Brazil real; T2DM, type 2 diabetes mellitus; RR, relative risks; SFr, Swiss francs; VPA, vigorous physical activity.

Table 3 Characteristics of studies that applied an econometric approach to estimating the direct healthcare costs of physical inactivity (n=17)

First author and year of publication	Country	Data sources	Design	Sample	PA categories	Types of costs	Covariates adjusted	Major findings	Population-level amount* (%)†, sensitivity/uncertainty analysis	Time frame‡	Funding/COI
Anderson 2005[59]	USA	HeathPartners members survey (1995) linked with administrative healthcare claim data (1996–1999)	Cross-sectional	Members ≥40 years of age (n=4674)	≥4×30 min/week (yes vs no)	Professional and hospital claims	Age, sex, chronic disease, smoking, BMI	Physical inactivity, overweight and obesity were associated with 23% health plan charges and 27% of national healthcare charges	Statistical sensitivity analysis conducted	1 year (1997)	HealthPartners Center for Health Promotion/COI statement missing
Andreyeva 2006[35]	USA	Health and Retirement Study	Longitudinal	Adults aged 51–61 years and their spouses (n=7338)	Any VPA versus no VPA	Total healthcare cost	Baseline healthcare spending, socio-demographics, chronic health conditions, smoking, alcohol, BMI	PA was associated with a 7.3% reduction in healthcare cost over 2 years	Structural and statistical sensitivity analysis: 13.2% reduction when baseline health was not adjusted	1 year (2004)	No funding reported/COI statement missing
Aoyagi 2011[42]	Japan	Nakanojo Study	Cross-sectional	All willing community residents aged ≥65 years (not severely demented or bedridden; n=5200)	Quartiles based on accelerometer and pedometer Q1=2000 steps/day and 5–10 min/day of activity at >3 METs	Insurance payments for treatment by a doctor or outpatient service of a hospital (no inpatient treatment cost)	Not stated	Increase in PA of 5% of each group by a single ranking leads to 3.7% of total medical expense		1 year (2009)	Japan Society for the Promotion of Science/no COI declared
Brown 2008[43]	Australia	ALSWH 2001	Cross-sectional	Women participants aged 50–55 years (n=7004)	High: ≥1200 MET.min/week Moderate: 600–<1200 MET.min/week Low: 240–<600 MET.min/week Very low: 40–<240 MET.min/week None: <40 MET.min/week	Australian Medicare System (outpatient, general practitioner, specialist, and others)	Area of residence, education, smoking, alcohol	Costs were 26% higher in inactive than in moderately active women, and 43% higher in inactive and obese women than in healthy weight, moderately active women	Potential population-level savings: increasing from 'none' to 'low' without changing BMI: $A39.1 million, with change in BMI: $A47.1 million	1 year (2001)	Australian Government Department of Health and Ageing/COI statement missing
Carlson 2014[5]	USA	NHIS 2004–2010, MEPS 2006–2011	Cross-sectional	Adults aged ≥21 years (non-pregnant, did not respond unable to do PA; n=51 165)	Active: ≥150 min MVPA/week Insufficiently active: >0–<150 min MVPA/week Inactive: 0 MVPA	Expenditures for all services	Age, sex, race/ethnicity, marital status, census region, area, poverty level, health insurance, education, smoking, BMI	Mean annual difference in inactive adults (compared with active) was US$1437 (29.9%) and in insufficiently active US$713 (15.4%).	Physical inactivity accounted for US$131 (91–172) billion (12.5%), US$117 (76–158) billion (11.1%) after adjusting for BMI; multiple structural and statistical sensitivity analyses, eg, after excluding those with difficulty walking: US$90 (58–122) billion (9.9%); and further adjusted for BMI: $79 (46–112) billion (8.7%) Converted national estimate: $132.9 billion INT	1 year (2012)	No funding reported/no COI declared

Continued

Table 3 Continued

First author and year of publication	Country	Data sources	Design	Sample	PA categories	Types of costs	Covariates adjusted	Major findings	Population-level amount* (%)†, sensitivity/uncertainty analysis	Time frame‡	Funding/COI
Chevan 2014[46]	USA	NHIS 2006–2007, MEPS 2007–2009	Cross-sectional	Non-disabled adults (did not respond unable to do PA; n=8843)	(1) PA guidelines (strength and/or aerobic PA) (2) Aerobic PA (0; <75; 75–149, 150–299, >300 min/ week)	Expenditures for all services	Age, sex, race, income, health status	No significant association between PA and expenditure when adjusted for covariates		1 year (2012)	No funding reported/No COI declared
Cho 2011[39]	Korea	A study of 250 adults	Cross-sectional	Adults aged ≥ 40 years, selected from community centres (n=250)	Inactive versus acceptable versus active based on questionnaire score	Self-reported healthcare visits and direct expenditure	None	The mean difference between active and inactive persons was US$14.12/month		1 year (2009)	Korean Government/COI statement missing
Codogno 2015[48]	Brazil	Local municipality health offices healthcare expenditure data	Cross-sectional	Adults randomly selected in five basic healthcare units in Bauru (≥50 years; n=963)	Habitual PA questionnaire score quartiles	Overall healthcare expenditure (all items registered in the medical records)	Age, sex, smoking, blood pressure, BMI	Inverse association between PA and expenditure	PA explained 1% of medicine and 0.7% overall expenditure (statistical sensitivity analysis conducted)	1 year (2010)	Brazilian Government and Brazilian Ministry of Science and Technology/ no COI declared
Lin 2008[45]	Taiwan	NHIS 2001, National Health Insurance Research Database 2001	Cross-sectional	Adults selected from three major regions of Taiwan (n=15 670)	Exercised in the past 2 weeks (yes versus no)	Healthcare claim data (inpatient and outpatient)	Age, sex, ethnicity, marital status, employment status, income, education,	Those who exercised had lower inpatient expenses (2079 vs 3330 NT$) but higher outpatient expenses (9738 vs 9151 NT$)		1 year (2001)	Taiwan's National Science Council/COI statement missing
Min 2016[38]	Korea	Korean National Health Insurance Database	Retrospective cohort	40 to 69-year-old adults who had not changed PA levels during the study period (n=47 290)	Continuously reported exercise that 'worked up a sweat' for >1 time/week	Inpatient, outpatient and prescription costs	Age, sex, income, area of residence, smoking, alcohol, BMI (propensity score matching)	Those who were continuously inactive had 11.7% higher medical costs (8.7%–25.3% disease specific)		Multiple years (2005–2010)	National Research Foundation of Korea and Seoul National University Hospital/no COI declared
Musich 2003[44]	Australia	AHMG Insurance Claim Health Risk Appraisal data (1995–1999)	Cross-sectional	AHMG members (n=19 812)	≤60 min/week (at risk) versus >60 min/ week	Claim charges, primarily including inpatient and some ancillary services	None	At risk versus not at risk: $460 versus $A423/year (not statistically significant)		2 years (1995–1999)	No funding reported/COI statement missing
Peeters 2014[36]	Australia	ALSWH and Medicare system (2001–2010)	Longitudinal	Middle-aged cohort (born 1946–1951) of Australian women (n=5535–6108)	(1) Active (≥40 MET-min/day)/low sitting (<8 hours/day) (2) Active/high sitting (3) Inactive/ low sitting (4) Inactive/high sitting	Total Medicare cost paid by the government and out of pocket	Survey year, marital status, area of residence, education, smoking, BMI, depressive symptoms	Physical inactivity, not prolonged sitting was associated with higher costs ($A94/year)	$A40 million at the national level	1 year (2010)	Australian Government Department of Health and Ageing and Australian National Health and Medical Research Council/ no COI declared
Pratt 2000[40]	USA	NMES 1987	Cross-sectional	Non-pregnant participants aged ≥15 years, without physical limitations (n=20 041)	≥30 min of MVPA over ≥3 days versus the rest of the sample	Self-reported medical costs confirmed by a survey of medical providers	Age, sex, lifetime smoking status	Lower annual direct medical costs among those who are physically active: US$1019 versus US$1349	US$29.2 billion, statistical sensitivity analysis conducted Converted national estimate: $103.6 billion INT	1 year (1987)	No funding reported/COI statement missing

Continued

Table 3 Continued

First author and year of publication	Country	Data sources	Design	Sample	PA categories	Types of costs	Covariates adjusted	Major findings	Population-level amount* (%)†, sensitivity/uncertainty analysis	Time frame‡	Funding/COI
Pronk 1999[47]	USA	HeathPartners members survey (1995) linked with administrative healthcare claim data (1995–1996)	Cross-sectional data	Members ≥40 years of age (n=5689)	Number of active days in the prior week	HealthPartners medical claims	Age, sex, race, chronic disease, smoking, BMI	An additional day of PA led to a 4.7% decrease in median medical charges		1.5 years (1995–1996)	HealthPartners/COI statement missing
Wang 2004[41]	USA	NMES 1987	Cross-sectional	Non-pregnant adults who reported being downhearted and blue at least a little of the time (n=12 250)	≥30 min of MVPA over ≥3 days versus the rest of the sample	Medical costs including hospitalisations, physician visits, medication, home care	Age, sex, race, socioeconomic status, area of residence, physical limitations, smoking, body weight	Among those downhearted and blue, physical inactivity was associated with 6.1% of the expenditure (US$133 in 1987 and US$429 in 2003)	Physical inactivity accounted for US$11.8 billioConverted national estimate: $37.2 billion INTn in 1987 (US$38 billion in 2003) among those who were downhearted and blue	1 year (1987/2003)	No funding reported/COI statement missing
Wang 2004[49]	USA	NHIS 1995, MEPS 1996	Cross-sectional	Non-pregnant adults without physical limitations (n=2472)	≥5×30 min MPA/ week or ≥3×20 min VPA versus the rest of the sample	Self-reported medical costs confirmed by a survey of medical providers	Covariates were not specified, stratified by age groups, sex, smoking status and weight	Active adults and lower prevalence of CVD and lower cost per case of CVD	Physical inactivity accounted for 13.1% of medical expenditure of people with CVD	1 year (1996)	No funding reported/COI statement missing
Yang 2011[37]	Japan	A cohort of the National Health Insurance beneficiaries	Longitudinal	Seniors aged ≥70 years capable of PA, without CVD, cancer, arthritis, and cognitive dysfunction (n=483)	Low: no sports+ no brisk walking + low walking Moderate: no sports + no brisk walking + any walking High: any sports + any brisk walking + any walking	Inpatient and outpatient costs	Age, sex, hypertension, hyperlipidaemia, diabetes, liver or renal disease, smoking, drinking, BMI, physical performance, depressive symptoms, cognitive status	Per capita medical costs: low versus moderate versus high: US$875 versus US$751 versus US$723/month; when adjusted for physical performance: US$827 versus US$711 versus US$702/month (difference driven by inpatient costs)	Statistical sensitivity analysis conducted	5.5 years (2002–2008)	Japanese Society for Promotion of Science, Japan Atherosclerosis Prevention Fund, Ministry of Health, Labour and Welfare of Japan/COI statement missing

*Converted national estimate: we inflated the national estimates in local currency units from the year of data to 2013 using the annual consumer prices inflation indicators from the World Bank (http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG) and then converted to purchasing power parity (PPP) international dollars using conversion factors provided by the World Bank (http://data.worldbank.org/indicator/PA.NUS.PPP).
†Interpreted as the total amount of direct healthcare cost that was associated with physical inactivity. % interpreted as the percentage of overall healthcare cost that was spent on diseases that were attributable to physical inactivity.
‡The cost estimate may be based on data from multiple years; however, the time frame here refers to the year for which the estimate is presented. For example, Anderson 2005[59] averaged annualised charges over a 4-year period (from 1996 to 1999) but presented the estimates in 1997 US$.
A, Australian dollars; AHMG, Australian Health Management Group; ALSWH, Australian Longitudinal Study on Women's Health; BMI, body mass index; COI, conflict of interest; CVD, cardiovascular disease; INT, International dollars; MEPS, Medical Expenditure Panel Survey; MET, metabolic equivalents; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; NHIS, National Health Interview Survey; NMES, National Medical Expenditure Survey; NT$, New Taiwan dollars; PA, physical activity; Q1, quartile 1; VPA, vigorous physical activity.

Table 4 Characteristics of studies that estimated the indirect costs of physical inactivity

First author and year of publication	Country	Data sources	Definition of PA (minimal risk counterfactual)	Types of indirect costs	Methodology	Findings* (sensitivity analysis)	Time frame	Discounting costs
Cadilhac 2011[27]	Australia	National Health Survey 2004–2005, Australian Burden of Disease data 2003, Time Use Survey 2006	≥5×30 min MPA or ≥3×20 min VPA /week	Work-forced, home-based and leisure-based production	Workforce production: Friction Cost Approach (Human Capital Approach as sensitivity analysis); household production: 'replacement cost'; leisure time production: 'opportunity cost method' approach	$A1135 million, structural and statistical sensitivity analysis conducted Converted national estimate: $882.8 million INT	Lifetime	Yes
Ding 2016[2]	142 countries	International Labour Organization employment statistics, Global Burden of Disease Study 2013, World Bank 2013 gross domestic product data	≥150 min/week of MVPA	Productivity losses due to premature mortality	Friction Cost Approach (Human Capital Approach as sensitivity analysis)	$13.7 billion INT worldwide, structural and statistical sensitivity analysis: $3.5–34.5 billion INT, when using unadjusted PAFs: $21.3 ($6.1–47.6) billion INT	1 year (2013)	N/A
Janssen 2012[18]	Canada	Canadian Health Measures Survey 2007–2009, EBIC 2000	7-day accelerometry ≥150 min/week	Productivity losses due to illness, injuries/disability and premature deaths	Human Capital Approach	$C4.3 billion, statistical sensitivity analysis: $C2.8–6.1 billion Converted national estimate: $3.8 billion INT	Lifetime	Yes
Katzmarzyk 2004[20]	Canada	CCHS 2000–2001, EBIC 1998/93	Energy expenditure ≥6.3 kJ/kg/day	Productivity losses due to illness, injuries/disability and premature deaths	Human Capital Approach	$C3.7 billion, statistical sensitivity analysis±20% Converted national estimate: $3.8 billion INT	Lifetime	Yes
Katzmarzyk 2011[19]	Canada	CCHS 2009, EBIC 1998	Energy expenditure ≥6.3 kJ/kg/day	Productivity losses due to illness, injuries/disability and premature deaths	Human Capital Approach	$C2.3 billion in Ontario, Canada	Lifetime	Yes (based on checking the reference)
Krueger 2014[23]	Canada	CCHS 2009, EBIC 1998	Not defined as 'inactive' (did not specify)	Productivity losses due to illness, injuries/disability and premature deaths	Human Capital Approach	$C7 billion, statistical sensitivity analysis conducted Converted national estimate: $5.8 billion INT	Lifetime	Yes (based on checking the reference)
Krueger 2015[22]	Canada	CCHS 2012, EBIC 1998/2008	Leisure-time energy expenditure ≥1.5 kcal/kg/day	Productivity losses due to illness, injuries/disability and premature deaths	Human Capital Approach (Friction Cost Approach as sensitivity analysis)	$C7.5 billion, structural sensitivity analysis conducted: much lower estimates based on Friction Cost Approach Converted national estimate: $6.2 billion INT	Lifetime	Yes (based on checking the reference)
Krueger 2016[21]	Canada	CCHS 2012, EBIC 1998/2008	Leisure-time energy expenditure ≥1.5 kcal/kg/day	Productivity losses due to illness, injuries/disability, and premature deaths	Human Capital Approach	$C673.5 million for British Columbia, Canada, quoted previous statistical sensitivity analysis±17%	Lifetime	Yes (based on checking the reference)
Martin 2001[25]	Switzerland	Health-enhancing PA survey 1999, a published study on costs associated with each disease, accident statistics from the Swiss Council for Accident Prevention	5×30 min MPA or 3×20 min VPA /week	Productivity losses for cardiovascular disease, type 2 diabetes and back pain only	Human Capital Approach	1.4 billion SFr, structural sensitivity analysis conducted Indirect cost of sports accidents: 2.3 billion SFr	Lifetime	N/A

Continued

Table 4 Continued

First author and year of publication	Country	Data sources	Definition of PA (minimal risk counterfactual)	Types of indirect costs	Methodology	Findings* (sensitivity analysis)	Time frame	Discounting costs
Zhang 2013[26]	China	Chinese Behavioral Risk Factors Surveillance 2007, National Health Services Survey 2003	5×30 min MPA or 3×20 min VPA /week	Economic output lost because of illness, injury-related work disability or premature death before retirement	Human Capital Approach	US$3.3 billion Converted national estimate: $8.5 billion INT	Lifetime	Not stated
Grey literature								
Market Economics Limited 2013[24]	New Zealand	Various sources including the Ministry of Health, Statistics New Zealand, District Health Board reports, and others	≥30 min PA×5 days/ week	Monetary values for loss of productivity, pain and suffering. Also included other costs, such as promoting PA	Value of a statistical life/life years approaches	$661 million NZD, structural sensitivity analysis: $295 million–7.5 billion NZD Converted national estimate: $499.9 million INT	Lifetime	Yes
Colman 2004[16]	Canada	CCHS, EBIC 1998	Expenditure ≥1.5 kcal/ kg/day	Productivity losses due to premature death and disability	Human Capital Approach	$C362 million/year for British Columbia, Canada	Lifetime	Yes (based on checking the reference)
International Sports and Culture Association and Centre for Economics and Business Research 2015[17]	EU-28	WHO, Organisation for Economic Cooperation and Development, Eurostat, International Development Association, EUCAN and published studies	150 min MPA or 75 min VPA/week or combination	Value of human capital that is lost due to premature morbidity and mortality	Human Capital Approach	UK: €12.31 billion; Germany: €12.85 billion; Italy: €10.58 billion; France: €8.25 billion; Spain: €5.62 million; Poland €1.96 million; EU-28: €71.1 billion Converted national estimates: UK $15.5; Germany $16.8; Italy $14.4; France $10.2; Spain $8.5; Poland $4.7 billion INT	Lifetime	Not stated

*Converted national estimate: we inflated the national estimates in local currency units from the year of data to 2013 using the annual consumer prices inflation indicators from the World Bank (http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG) and then converted to purchasing power parity (PPP) international dollars using conversion factors provided by the World Bank (http://data.worldbank.org/indicator/PA.NUS.PPP). However, the estimate was not converted for Martin et al[25] due to the lack of SFr to PPP international dollar conversion factor from the World Bank.

A, Australian dollars; C, Canadian dollars; CCHS, Canadian Community Health Survey; EBIC, Economic Burden of Illness in Canada; EU-28: 28 member countries of the European Union; INT, international dollars; MPA, moderate physical activity; N/A, not applicable; NZD, New Zealand dollars; PA, physical activity; PAF, population attributable fraction; £ , pounds sterling; SFr, Swiss francs; VPA, vigorous physical activity.

with a substantial disease burden in almost every country where estimates exist. However, because of large variation in methodologies, health systems and the prevalence of physical inactivity over time, it is problematic to compare estimates of the cost of physical inactivity across studies and countries. As demonstrated by the current review, there is important variation in the perspective taken (eg, healthcare payer only vs societal perspective), type of costs included, specific costing approaches, measurement of physical activity, adjustment for covariates/confounding, time frame (eg, 1 year vs lifetime) and whether sensitivity analysis was undertaken and in what form. These all contributed to the substantial variations in the estimates of economic burden.

Study perspective

The perspective refers to the viewpoint from which an economic analysis is conducted, which influences the types of information included.[50] Both the original and second Panels on Cost-Effectiveness in Health and Medicine recommended taking a societal perspective as the most comprehensive approach because it estimates the total impact on society, including the health sector, non-health sector and households.[50 51] Economic burden of disease studies should ideally be aligned with this guidance for consistency. Specifically, studies should collect information on costs to the healthcare sector (ie, direct costs to public/private healthcare providers and patient costs), non-health sectors (indirect costs or productivity losses) and household economy (eg, impact on usual activities and carers, where appropriate). Most existing studies on physical inactivity take a narrower healthcare sector perspective with the rationale that the key decision maker in addressing inactivity is the health sector. While studies on healthcare costs are necessary, we argue that it is not sufficient, and it is straightforward to estimate non-health sector productivity losses and the impact on the household economy. Taking such wider impacts into account can help make the economic case for additional healthcare resources. Furthermore, policies and interventions that impact on physical activity may reside outside of the healthcare sector (eg, transportation) and may involve cross-sectoral partnership.

It is important to note that this approach estimates the 'production costs' resulting from physical inactivity to society, regarding the increase in healthcare production and the reduction in economy and household production. As discussed previously, it is possible to build on this to 'value' the impact of inactivity on health, rather than only estimating cost. There are alternative methods to do so, such as willingness to pay and VSL; however, these methods can be expensive to undertake. Therefore, in an effort to proceed incrementally and pragmatically, and to attempt to bring some initial alignment of future economic burden of disease studies, we reiterate our recommendation to take a societal approach concentrated on production costs and to disaggregate results into healthcare sector (direct costs), the wider economy or productivity impacts (indirect costs) and the household economy.

PAF-based versus econometric approaches

Two main approaches were used for estimating the direct healthcare costs of physical inactivity: a PAF-based approach and an econometric approach. Usually, an econometric approach leads to higher estimates. The marked differences in estimates using the two approaches may be explained in part by the following. First, a PAF-based approach focuses on capturing costs averted if certain diseases were prevented. Econometric models could additionally take into account potentially higher treatment intensity and costs, and possibly other ancillary costs among those with a disease/condition.[52] Second, although the US Physical Activity Guidelines Advisory Committee Report[28] concluded that there is moderate to strong evidence for the effects of physical activity on more than 20 diseases/conditions, most studies using a PAF-based approach included only a small subset of these. For example, no study reviewed included more than eight conditions (table 2). Therefore, using a PAF-based approach may underestimate the real healthcare costs associated with physical inactivity. Third, econometric analyses may capture differences in healthcare expenditure resulting from the fundamental differences between physically active and inactive individuals, such as overall health-seeking behaviour and health status. For example, according to Carlson *et al*'s cross-sectional analysis, adjusting for body mass index and excluding those with difficulty walking led to a 40% reduction in the estimated healthcare costs of physical inactivity.[5] Fourth, while studies using a PAF-based approach were mainly based on overall adult populations, most studies using an econometric approach were based on samples of older participants, where physical inactivity-related diseases and conditions were more likely to occur. Furthermore, in the longitudinal analysis by Andreyeva and Sturm, adjusting for baseline health led to 45% lower healthcare cost estimates.[35] Although most econometric analyses adjusted for covariates, which should be standard practice, without longitudinal data and careful methodological considerations, it is likely that econometric models could overestimate the actual healthcare costs of physical inactivity because of residual confounding and reverse causality.

The choice of applying a PAF-based approach versus an econometric approach depends mainly on data availability. Econometric analyses require data on physical inactivity and healthcare expenditure linked at the individual level. Regression models are usually performed to estimate the excess healthcare expenditure among those who are physically inactive, which could then be extrapolated to a population. Econometric analyses also provide opportunities to estimate healthcare costs within a particular population subgroup, for example, those who were 'downhearted and blue'.[49] However, it is important to ensure the generalisability of a sample before extrapolating findings to an entire population.

Studies using a PAF-based approach require data on healthcare costs for each of the diseases/conditions associated with physical inactivity. By applying PAF, one can estimate the proportion of healthcare costs attributable to physical inactivity. Several methodological aspects should be considered. First, the calculation of PAF should be based on adjusted RR. Unfortunately, more than half of the studies tabulated in table 2 did not adjust for covariates for PAF calculation. In our previous international study, we conducted a sensitivity analysis by applying PAF based on unadjusted RR. We found that this nearly doubled the estimates from the main analysis that was based on adjusted PAF.[2] Second, ideally for calculating PAF, RR and the prevalence of physical activity should be based on the same population using the same definition of physical activity. However, this is challenging because the current epidemiological evidence of physical activity mostly stemmed from a small number of countries using heterogeneous definitions and measurement of physical activity. Third, summing physical inactivity-related costs of each disease/condition may result in double counting due to comorbidity. Current studies rarely address this issue, leaving comorbidity an ongoing challenge for future methodological advancement.

Although the decision for methodological approaches is practically driven by data availability, it is vital that for whatever approach chosen, care is taken to address the methodological

issues raised above and to report all key assumptions, limitations and justifications for approaches taken.

Estimates of indirect costs

Only one-third of studies estimated the indirect costs in addition to direct costs. Studies varied depending on whether an FCA, HCA or VS approach was taken, which naturally results in different estimates produced. For example, according to the 1998 Economic Burden of Illness in Canada report, which applied an HCA, indirect costs of cardiovascular disease represented 171% of its direct costs.[53] However, the same ratio was merely 3.1% according to the 2008 report,[54] which applied an FCA.[22]

It is important to recognise that the existence of the FCA, HCA and VSL approach is not a weakness of economic analysis. Each approach involves different value judgements regarding what the analysis should consider, such as the cost of replacement (to employers), lifetime (to employees) or the value of life itself. These are ethical and contestable concepts. We recommend that a transparent economic analysis should explicitly state the value frame used and assumptions made and calibrate the analysis to the intended decision makers/end-users. As part of this process, we recommend structural sensitivity analyses that adopt different approaches, similar to the study by Cadilhac *et al*[27] to enable readers to fully understand the impact of adopting different value judgements. Equally, it is important that those who interpret the estimates understand the differences between methods to avoid erroneous comparisons between studies and to avoid needless confusion. It is important that economists are part of research teams to guide the analysis undertaken and help communicate the methods and results.

Time frame

The economic burden of physical inactivity could occur at present and in the future. For example, deaths and disability due to illnesses could incur future costs in terms of losses of income and other production. Almost all studies reviewed used a 1-year time frame for direct costs to capture healthcare expenditure occurring in the year of analysis. Studies that included indirect costs adopt a lifetime approach by default, by valuing productivity losses in the present period and also in the future (for the FCA this is conditional on the replacement period). It is important that studies explicitly describe the time frame of the analysis and apply discounting to estimate the NPV of all current and future estimates. The NPV is a single estimate designed to create a consistent comparison across studies that may use different time periods.[15 50] A number of studies estimated lifetime costs did not use or explicitly mention discounting. This is poor practice that can be easily avoided.

Sensitivity analysis

Estimating the economic burden of physical inactivity, or any other risk factor, involves both inevitable statistical uncertainty and making various choices regarding which modelling approaches/methods (eg, FCA vs HCA) are included in the study. Therefore, it is imperative to clearly state assumptions for the main analysis and conduct comprehensive sensitivity analyses.[11 50 51] Sensitivity analysis is an integral component of any robust and transparent economic analysis.[55] Based on the current review of the literature, sensitivity analysis was not included in all studies. Again, this should be standard practice.

Study presentation

Most studies presented the results with sufficient information regarding the source of data, sampling frame (if applicable), measures of physical activity, type of costs, diseases/conditions included and year and currency. However, presentation of other methodological details was insufficient and often ambiguous, such as how the PAF was derived (eg, whether based on adjusted RR), perspectives, approaches, time frame, discounting and sensitivity analysis. Several studies presented the proportion of total healthcare expenditure attributable to physical inactivity, which is meant to facilitate comparison across studies and countries/regions. However, some studies presented such information in a misleading way by summing direct and indirect costs as the numerator, which inflated the percentage by several fold.[17 18] Future studies should clearly and accurately present key information to improve transparency and integrity.

The need for economic evaluation of interventions to address physical inactivity

Estimating the economic burden is a vital first step in understanding the overall burden of physical inactivity and the consequences of inaction, which helps galvanise policy efforts. However, burden of disease studies should not be the sole consideration in the prioritisation process. For instance, large problems may be addressed relatively inexpensively and vice versa. Therefore, it is vital that economic evaluation is undertaken to assess both the costs and benefits of interventions to reduce the economic burden and to identify interventions that are the greatest value for money. In this way, resource-constrained decision makers can best prioritise societal resources to increase population health. There are guidelines that should be followed when conducting and reporting economic evaluations.[56]

Future directions

Overall, estimating the economic burden of physical inactivity is an area of increasing research and policy importance. We recommend that future cross-disciplinary collaborations involve economists to ensure that best practice is adopted, and physical activity experts to ensure that analyses are valid. Specifically, we recommend that a societal perspective is adopted to include direct, indirect and household costs, with the overall estimate reported and then disaggregated to these three levels. Furthermore, it is vital to carefully consider potential confounding, reverse causality and comorbidity. Discounting (when future impacts are included) and sensitivity analysis should be undertaken routinely. Overall, it is vital that studies are transparent in reporting the objectives, rationale and intended end-users/decision makers and that they align with assumptions made with the objectives. Finally, studies should transparently report any funding sources and conflict of interest.

There are currently no guidelines specifically for studies that estimate the economic burden of risk factors; therefore, we have summarised what we have discussed above in a new checklist (table 5), adapted from the Consolidated Health Economic Evaluation Reporting Standards.[56] It is important to acknowledge that it is impossible to completely standardise methodologies because economic analysis is often conducted to address the needs of specific stakeholders. Hence, our newly developed checklist should be used as a guide for improving methodological rigour and reporting quality for future economic analysis that is set up to appropriately address specific objectives.

Assessing the economic burden of physical inactivity is important; however, there is a need for general improvement in

Table 5 Checklist for reporting estimates of the economic costs/burden of risk factors*

Section/item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an estimate of the economic burden of a risk factor (ie, physical activity) and identify the study sample.	
Abstract	2	Provide a summary of objectives, perspective, setting, methods (including study design and inputs), results, including statistical uncertainty, and sensitivity analysis (changes in key structural assumptions) and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the study objective(s) and broader context for the study. Present the study question and its relevance for health policy or practice decisions. Describe whether previous estimates existed for the same risk factor among the same (or comparable) populations.	
Methods			
Target population and subgroups	4	Describe characteristics of the study sample/population. If subsamples/populations are chosen, provide justification of why and how they are chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made. Define decision maker(s) that the study is intended to inform.	
Study perspective	6	Describe the perspective of the study, ensure this is consistent with the study objective(s) and aligned with the categories of costs/burden being evaluated.	
The risk factor(s)	7	Define the risk factor(s) (eg, physical inactivity), how the risk factor is measured (eg, questionnaire), the reliability and validity of the measurement instrument, the minimal risk counterfactual and the rationale for selecting the counterfactual or categories (eg, meeting physical activity recommendations).	
Choice of health outcomes	8	Define the health outcomes associated with the risk factor(s), the rationale for selecting the outcomes (eg, evidence on the risk factor–outcome associations), describe whether comorbidity is taken into account.	
Costs/burden estimated	9	Define the costs/burden estimated (eg, healthcare expenditure, productivity losses) and the estimates included (eg, inpatient and outpatient care).	
Data sources	10	Describe the sources of data, the years the data cover and any major caveats/limitations related to the data, if any.	
Time frame	11	State the time frame over which costs/burden are considered (eg, single year, patient lifetime) and explain why it is appropriate.	
Discount rate(s)	12	Report the choice of the discount rate(s) used for costs/burden and explain why this choice is appropriate.	
Year of reporting and common unit of measure for costs/burden	13	Report the year that the estimates refer to and the common unit of measure used to collate costs/burden (eg, for costs state the currency, and for burden state the health measure, such as disability adjusted life years. If relevant, describe methods for converting costs into a common currency and year of reporting (eg, inflation rates, purchasing power parity conversion factors).	
Analytic methods and assumptions made	14 14a 14b	Describe the overall analytical approach (eg, population attributable fraction (PAF) approach and econometric approach). Describe all assumptions, such as rationale for choice of model, statistical distribution and any other major assumptions (eg, missing data imputation). For study using a PAF approach, report where the PAF was derived, whether PAF was based on adjusted or crude relative risk. For study using an econometric approach, report the study design (eg, prospective, cross-sectional), statistical models and covariates adjusted.	
Results			
Costs/burden estimates	15	Report the values (eg, mean) and associated statistical distributions/ranges for all parameters. If secondary data is used, reference appropriately. A bespoke table transparently reporting all input values (from methods) and outputs (from results) is strongly recommended.	
Characterising uncertainty	16	If applicable, describe the effects of sampling uncertainty (statistical sensitivity analysis) on results and structural uncertainty in changing methodological assumptions (eg, study perspective, model choice and discount rates).	
Characterising heterogeneity	17	If applicable, report differences in costs and/or other outcomes that can be explained by variations between subgroups with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Other			
Source of funding	18	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.	
Conflict(s) of interest	19	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors to comply with International Committee of Medical Journal Editors' recommendations.	

*Checklist adapted from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).

the conduct, reporting and interpretation of studies to increase the credibility of findings and to promote their use by decision makers.

What is currently known?

- The pandemic of physical inactivity causes diseases and deaths and costs billions of dollars to societies around the world.
- Economic analysis is essential to bridging the policy–implementation gap, increasing political engagement and motivating actions.
- A range of studies have been published on the economic burden of physical inactivity, mostly in developed countries. However, prior estimates, even for the same country, vary substantially across studies.
- There is no existing quality assessment tool or established methodological guidelines on how to conduct a high-quality analysis of the economic burden of physical inactivity or other lifestyle risk factor.

What are the new findings?

- Among the current economic burden estimates, there is important variation in the perspective taken, type of costs included, specific costing approaches, measurement of physical activity, adjustment for covariates/confounding, time frame and whether sensitivity analysis was undertaken and in what form. These all contributed to the substantial variations in the estimates of economic burden.
- Two main approaches were used for estimating the direct health care costs of physical inactivity: a population attributable fraction-based approach and an econometric approach. Usually, an econometric approach leads to higher estimates based on fundamental differences between the two approaches.
- Many prior studies did not follow best practice in economic analysis and did not present sufficient information in a transparent fashion.
- We developed a new checklist as a guide for improving methodological rigour and reporting quality for future economic burden analysis, adapted from the Consolidated Health Economic Evaluation Reporting Standards checklist.

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The economic burden of physical inactivity: a systematic review and critical appraisal

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BRIEF REPORT

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Evaluation of the Cancer Council NSW *Eat It To Beat It Healthy Lunch Box* Sessions: A short intervention to promote the intake of fruit and vegetables among families of primary school children in NSW Australia

Abstract

Issue addressed: Children and adults in Australia are not eating the recommended amounts of fruits and vegetables. Our objective was to assess the effectiveness of a health promotion intervention to improve fruit and vegetable intake among primary school children and their families in NSW.

Methods: The Cancer Council New South Wales *Healthy Lunch Box* sessions were a 25-minute session delivered to parents of primary school-aged children. The sessions provided information and resources about fruit and vegetables and healthy school lunch boxes. The evaluation is a quantitative uncontrolled pre-post design. Data were collected using three questionnaires, pre-intervention, 1 week post-intervention and 6 months post-intervention.

Results: A total of 204 parents completed all three evaluation questionnaires to 6 months. Knowledge of recommended intakes and serving sizes of fruit and vegetables improved significantly after the intervention. There was an increase in parents reporting packing vegetables (often/always) in the child's lunch box at 1 week (47%) and 6 months post-intervention (40%) compared to pre-intervention (32%). The proportion of parents reporting that they were confident in packing a healthy lunch box increased from 45% pre-intervention to 62% after the intervention.

Conclusions: The *Healthy Lunch Box* sessions were effective in improving parental knowledge and practices related to fruit and vegetables and parental confidence with packing a healthy lunch box.

So what: This short intervention could be a useful component of a portfolio of interventions to support parents with knowledge and resources to pack a healthy lunch box for their children.

1 | INTRODUCTION

A diet high in fruits and vegetables assists in the prevention of chronic diseases and cancer.[1] In Australia, approximately 32% of cancers are caused by lifestyle factors, including low consumption of fruits and vegetables.[2,3] National data from 2014 to 2015 show that only 5.1% of Australian adults consume sufficient fruits and vegetables[4] and 73.1% of children aged 4-8 years consume adequate fruit while only 3.3% reported an adequate vegetable intake.[4] It is important to influence children's dietary intake as dietary behaviours often track into adulthood.[5,6] Health promotion interventions are needed to improve diet quality, particularly vegetable consumption for children and adults.[7]

The *Eat It To Beat It* program is multi-strategy community-based programme run by the Cancer Council New South Wales (CCNSW) to promote the intake of fruit and vegetables of families in NSW. One of the core intervention components is delivery of "*Healthy Lunch Box*" sessions by trained volunteers to parents of primary school students in NSW.

In this paper, we describe the *Healthy Lunch Box* intervention and the results of the evaluation. The evaluation assessed effectiveness in improving parental knowledge, self-efficacy and practices regarding increasing fruit and vegetables intake, particularly in regard to their children's lunch boxes, from pre-intervention to 1 week post-intervention, and the sustainability of effects to 6 months.

2 | METHODS

2.1 | Description of the *Healthy Lunch Box* intervention and evaluation design

The intervention is a free, 25-minute information session delivered to parents and carers of primary school-aged children in NSW, within the school setting. Volunteers are invited to attend a 1-day workshop where they are trained to deliver a standardised presentation developed by CCNSW. Details of the *Healthy Lunch Box* intervention messages and resources are given in Box 1.

To evaluate the intervention a simple pre-post evaluation design was used and focused on two regions in NSW: Hunter Central Coast (HCC) and Greater Western Sydney (GWS). There was no control group.

2.2 | Recruitment and consent procedures

Parent participation in the evaluation was voluntary and they were asked to provide written consent. Parents who consented were given 10-20 minutes to complete the pre-intervention paper-based questionnaire, prior to commencement of the 25-minute *Healthy Lunch Box* session.

BOX 1 Intervention components in the *Healthy Lunch Box sessions*

1. **Intervention messages**
   a. The link between poor nutrition, especially low fruit and vegetable intake, and risk of chronic disease,
   b. The fruit and vegetable guidelines for adults and children,
   c. Practical tips for healthy eating including a *Healthy Lunch Box* "equation" to encourage consumption of foods from each of the Australian Guide to Healthy Eating food groups,[8]
   d. Ways to limit consumption of unhealthy snack foods and encouraging water or milk as the best beverage choices to keep children hydrated.
2. ***Healthy Lunch Box* "show bag"** includes
   a. A weekly lunch box planner to attach to the fridge,
   b. A *Healthy Lunch Box* flip-book outlining an "equation" for packing foods from each food group in the lunch box and ideas on healthy choices from each of the food groups,
   c. Fruit- and vegetable-based snack ideas,
   d. A fridge magnet which outlines fruit and vegetables serve sizes,
   e. Resource showing photographs of individual serves of various fruits and vegetables and recommended number of serves by age group,
   f. Resource supporting the Crunch & Sip® program[9]

Post-intervention questionnaires were administered online at 1 week and 6 months post-intervention using Survey Monkey, and mailed paper-based questionnaires were sent to those without emails. A prize was used as an incentive to encourage participants to respond to the 6 month follow-up questionnaire.

2.3 | Questionnaire content

The questionnaire assessed knowledge, attitudes and practices with respect to fruits, vegetables and packing a healthy lunch box. Where possible existing validated questions from the Australian National Nutrition and Physical Activity Survey,[10] and questions from other evaluations of similar CCNSW programmes,[11] were used. Attitudes were generally assessed using a 5-point Likert scale, from "strongly agree" to "strongly disagree." Socio-demographic information was also collected.

The two post-intervention questionnaires were similar in content. They were designed to measure changes in knowledge of fruit and vegetables intakes and serving sizes, changes in parental self-efficacy for packing a healthy lunch box, and recall of the intervention messages.

2.4 | Statistical analysis

Statistical analysis was conducted with SPSS software version 22 (IBM Corp., Armonk, NY, USA). For categorical data, chi-square tests were used to assess the differences in proportions. McNemars' test was used for paired samples. To assess changes in knowledge, attitudes and practices between questionnaires, outcome variables were dichotomised and analysed with generalised estimating equation (GEE) models adjusting for socio-demographic factors. Differences were significant at the $P < .05$ level.

2.5 | Ethics

The protocol and consent procedures were approved by Sydney University Ethics Committee (HREC Reference Number 2014/828), the Catholic Schools Office Diocese of Broken Bay, Maitland-Newcastle, and Parramatta, and the Catholic Education Office Sydney.

3 | RESULTS

The *Healthy Lunch Box* sessions evaluated were in delivered in 54 schools in February-March 2015. A total of 535 parents/carers consented to the evaluation. The 1 week post-intervention questionnaire was completed by 394 parents/carers (75% response rate) and 204 completed the questionnaire at 6 months (38% of original respondents).

Table 1 shows the socio-demographic information from parents at pre-intervention, 1 week post-intervention and 6 months post-intervention. Study participants at 6 months were significantly more likely to be older, speak English as their main language, and be in the higher income bracket compared to those who dropped out of the study. There were no significant differences by employment, education or any other socio-demographic variables.

Table 2 shows the changes in parental knowledge of intervention messages among the 204 participants who completed all three questionnaires. The proportion of parents having correct knowledge of intervention messages significantly increased at 1 week post-intervention and almost all were also significantly different from pre-intervention after 6 months.

Most notably, there were significant increases in correct knowledge of vegetable intake guidelines, from 34% pre-intervention to 63% 6 months post-intervention and a significant increase in knowledge of the optimal drinks to pack in a child's lunch box (milk and water), from 60% pre-intervention to 89% 6 months post-intervention.

Table 2 also shows the parent's attitudes, opinions and practices in packing their child's lunch box. Fruits were regarded as both easy and important to pack in the child's lunch box by the majority of

TABLE 1 Socio-demographic characteristics of parents/carers participating in the *Healthy Lunch Box* evaluation

		Pre-intervention N = 535		1 week post-intervention N = 394		6 months post-intervention N = 204	
Characteristic		**N**	**Proportion (%)**	**N**	**Proportion (%)**	**N**	**Proportion (%)**
Region	Hunter Central Coast	224	41.9	175	44.4	90	44.1
	Greater Western Sydney	311	58.1	219	55.6	114	55.9
Age (years)*	<24	4	.7	1	.3	1	.5
	25-34	159	29.7	102	25.9	45	22.1
	35-44	306	57.2	239	60.7	122	59.8
	45+	64	12.0	52	13.2	36	17.6
Gender	Male	15	2.8	12	3.0	7	3.4
	Female	520	97.2	382	97.0	197	96.6
Education level*	Year 12 or less	120	23.3	82	21.4	40	20.1
	Undergraduate degree/certificate	289	56.2	221	57.6	120	60.3
	Postgraduate degree	105	19.6	81	21.1	39	19.6
Employment*	Employed	233	45.3	185	48.7	98	48.0
	Home duties	209	40.6	148	38.9	76	37.3
	Unemployed	39	7.6	26	6.8	13	6.4
	Other	33	6.4	21	5.5	17	8.3
Single parent household*	Yes	65	12.3	43	10.9	20	9.8
	No	458	86.4	346	88.0	182	89.2
Main language spoken at home	English	386	72.1	302	77.0	161	78.9
	Other	143	27.0	89	22.7	41	20.1
Aboriginal/Torres Strait Islander*	Yes	13	2.4	7	1.8	3	1.5
	No	515	96.3	383	97.5	199	97.5
Approximate household income per year AUD$	Less than 20 000	32	6.1	20	5.1	9	4.4
	20 000-39 999	32	6.1	23	5.9	14	6.9
	40 000-49 999	28	5.3	17	4.3	9	4.4
	50 000-69 999	67	12.7	47	12.0	26	12.7
	70 000+	239	45.3	194	49.5	103	50.4
	Don't know	40	7.6	21	5.4	7	3.4

*Some missing data for these variables.

parents pre- and post-intervention. Pre-intervention the majority of parents (91%) regarded it important to pack vegetables in their child's lunch box; this remained high post-intervention. There was a significant increase (15%) in parents often/always packing vegetables in the lunch box 1 week post-intervention compared to pre-intervention and some of this increase was maintained after 6 months. Parents' confidence in packing a healthy lunch box increased by 17% and importantly, 75% of parents perceived that attending the *Healthy Lunch Box* session had increased the amount of fruit and vegetables they and their family ate, 6 months post-intervention.

4 | DISCUSSION

The study has shown that the low-intensity and scalable 25-minute *Healthy Lunch Box* session was an effective intervention to deliver to parents of primary school students. The session increased parent's knowledge of fruit and vegetable guidelines and increased the vegetable content in children's lunch boxes. Other dietary messages emphasising that water and milk are the best two drinks for children may further encourage parents to provide these drinks instead of sugary drinks to their children. The intervention also increased parents' confidence with packing a healthy lunch box that their child would eat and enjoy. Six months post-intervention, three-quarters of parents/carers reported feeling that attending the *Healthy Lunch Box* session had increased the amount of fruit and vegetables they and their family ate.

Many Australians are unaware of how many fruit and vegetable serves they should eat each day[12] which may in turn affect the amount of fruits and vegetables they consume.[13,14] This evaluation showed a clear ceiling effect with regard to the packing of fruit in lunch boxes for children (above 93%); and this combined with the fact that in NSW 78% of school children already consume adequate

TABLE 2 Parental/carer knowledge of intervention messages 1 week and 6 months following the intervention compared to baseline (n = 204)

Knowledge	Percentage of participants with correct knowledge[a] (%)			Time effects Adjusted Odds Ratios[b] (95% confidence interval)			
	Pre-intervention	Post-1 week	Post-6 months	Post-1 week	*P*-value	Post-6 months	*P*-value
Knowledge of fruit serving sizes	48	73	68	3.25 (2.13, 4.96)	<.001	2.30 (1.56, 3.38)	<.001
Knowledge of fruit intake guidelines	49	76	68	3.82 (2.55, 5.72)	<.001	2.41 (1.64, 3.55)	<.001
Knowledge of vegetable serving sizes	37	52	53	1.90 (1.30, 2.78)	.001	1.97 (1.32, 2.96)	.001
Knowledge of vegetable intake guidelines	34	76	63	7.28 (4.81, 11.0)	<.001	3.88 (2.64, 5.68)	<.001
Fruit and vegetables decrease your risk of certain types of cancer	91	98	95	4.34 (1.65, 11.36)	.003	1.86 (.85, 4.07)	.12
Frozen, dried and canned fruit and vegetables are an acceptable alternative to fresh fruit and vegetables	53	82	77	4.76 (3.14, 7.23)	<.001	3.37 (2.24, 5.06)	<.001
Knowledge of best two drinks to pack in lunch box	60	92	89	8.51 (5.09, 14.20)	<.001	5.58 (3.59, 8.67)	<.001

Opinions/attitudes and practices	Percentage agreement[c] (%)			Time effects Adjusted Odds Ratios[d] (95% confidence interval)			
	Pre	Post-1 week	Post-6 months	Post-1 week	*P*-value	Post-6 months	*P*-value
Easy to pack fruit in lunch box	91	94	97	N/A		N/A	
Important to pack fruit in lunch box	100	100	100	N/A		N/A	
Often/always pack fruit in lunch box	93	95	96	N/A		N/A	
Easy to pack vegetables in lunch box	58	58	66	1.07 (1.07, 1.07)	.01	1.51 (1.51, 1.51)	<.001
Important to pack vegetables in lunch box	91	94	96	1.53 (.88, 2.67)	.13	2.29 (1.10, 4.75)	.03
Often/always pack vegetables in lunch box	32	47	40	2.10 (1.53, 2.87)	<.001	1.60 (1.14, 2.23)	.006
Confidence in packing a healthy lunch box	45	54	62	1.43 (1.07, 1.91)	.02	2.08 (1.47, 2.93)	<.001

N/A unable to generate output due to high baseline values and ceiling effects.

[a]Percentage of participants knowing the correct fruit/vegetable serving sizes or fruit/vegetable intake guidelines.

[b]Based on Generalised Estimating Equations, odds ratios for knowing the correct fruit/vegetable serving sizes or fruit/vegetable intake guidelines 1 week or 6 months following the intervention, compared to baseline. Odds ratios were adjusted for geographical region (Hunter Central Coast/Greater Western Sydney), having previously attended an Eat It to Beat It "Fruit and Veg sense" workshop, participant age, educational level (Year 12 or less/undergraduate degree or certificate/postgraduate degree), English being the main language spoken at home (yes/no), the number of children living at home and single parent household (yes/no).

[c]Percentage of participants agreeing or strongly agreeing with a given statement.

[d]Odds ratios for agreeing with knowledge/attitudes/opinion statements listed 1 week or 6 months following the intervention, compared to baseline. Odds ratios were adjusted for geographical region (Hunter Central Coast/Greater Western Sydney), having previously attended an Eat It to Beat It "Fruit and Veg sense" workshop, participant age, educational level (Year 12 or less/undergraduate degree or certificate/postgraduate degree), English being the main language spoken at home (yes/no), the number of children living at home and single parent household (yes/no).

fruit,[15] may suggest that further health promotion interventions to improve fruit intake may not be necessary.

Furthermore, this study showed that it is more difficult for parents to pack vegetables than fruit in a child's lunch box. Similar findings have been shown elsewhere[16] and data from the NSW Schools Physical Activity and Nutrition Survey (2015)[15] and national data confirm that children are much more likely to meet guidelines for fruit intake than vegetable intake.[4] This suggests that a focus on vegetables as a separate entity rather than as a combined entity with "fruits and vegetables" is needed to increase children's vegetable intake to meet Australian dietary guidelines for vegetables.[17,18]

Systematic reviews examining school-based programmes to improve fruit and vegetable intake and dietary intake in general have shown that multi-component interventions are most effective but that intensity of the intervention did not result in further improved intake in the longer term.[7,19,20] This is reinforced in our evaluation in which the positive effects of this low-intensity intervention were largely sustained for 6 months.

Unique aspects of the program were that targeted messages were delivered in a low-intensity/short session, delivered by trained volunteers and conducted in a familiar setting. Limitations included the lack of a control group, due to feasibility issues. Measures relied on parental self-report and more valid methods such as lunch box audits were not used[21]. Other limitations include the low response rates at 6 months and that parents who completed the study to 6 months were older, from English-speaking backgrounds and had higher incomes.

The intervention provides formative data concerning evaluation measures for low-intensity interventions such as the *Healthy Lunch*

Box session and illustrates that the intervention is acceptable in school settings. Although the focus of the *Healthy Lunch Box* sessions is on improving fruit and vegetable intake, consumption of less healthy foods and drinks is known to be high among school children in NSW and Australia,[15] so modification of the program to include messages about consumption of junk food and sugar-sweetened drinks may be beneficial. Another modification may be to train teachers or interested parents in delivery of the sessions, which may improve programme sustainability.

5 | CONCLUSION

The low-intensity *Healthy Lunch Box* sessions were effective in changing parental knowledge and self-efficacy with regard to the provision of fruit and vegetables to their children and families. The *Healthy Lunch Box* sessions are a useful component of a portfolio of interventions to support parents in providing healthier foods and drinks to their children.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Keywords
evaluation, fruit, healthy eating, interventions, lunch box, parents, vegetables

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Moving to an active lifestyle? A systematic review of the effects of residential relocation on walking, physical activity and travel behaviour

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ABSTRACT

Objective To synthesise the literature on the effects of neighbourhood environmental change through residential relocation on physical activity, walking and travel behaviour.

Design Systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PROSPERO registration number CRD42017077681).

Data sources Electronic databases for peer-reviewed and grey literature were systematically searched to March 2017, followed by forward and backward citation tracking.

Eligibility criteria A study was eligible for inclusion if it (1) measured changes in neighbourhood built environment attributes as a result of residential relocation (either prospectively or retrospectively); (2) included a measure of physical activity, walking, cycling or travel modal change as an outcome; (3) was quantitative and (4) included an English abstract or summary.

Results A total of 23 studies was included in the review. Among the eight retrospective longitudinal studies, there was good evidence for the relationship between relocation and walking (consistency score (CS)>90%). For the 15 prospective longitudinal studies, the evidence for the effects of environmental change/relocation on physical activity or walking was weak to moderate (CS mostly <45%), even weaker for effects on other outcomes, including physical activity, cycling, public transport use and driving. Results from risk of bias analyses support the robustness of the findings.

Conclusion The results are encouraging for the retrospective longitudinal relocation studies, but weaker evidence exists for the methodologically stronger prospective longitudinal relocation studies. The evidence base is currently limited, and continued longitudinal research should extend the plethora of cross-sectional studies to build higher-quality evidence.

INTRODUCTION

The health benefits of physical activity are well established.[1–4] However, globally, large proportions of the population are not sufficiently active or are completely inactive.[5 6] Walking is the most popular kind of physical activity[7 8] and typically occurs in neighbourhood environments, which may facilitate or hinder physical activity through their design.[9 10] Over the last two decades, there has been an exponential increase in studies which, based on social-ecological models of health,[11] have investigated the relationships between built environment attributes and physical activity, particularly walking.[12 13] This research has found that physical activity and walking are associated with a range of built environment attributes, such as walkability (street connectivity, land use mix and population density), access to green space and recreational facilities, safety from crime and traffic, aesthetics and access to public transport.[14–16] However, despite the substantial policy interest,[17–22] nearly all the studies in this field of research are cross-sectional[15 16 23] and therefore do not provide causal evidence about the effects of the built environment on physical activity. If cross-sectional studies report an association between environmental attributes, for example, walkability and physical activity, it is not clear to what extent this is due to the effect of the environment or to alternative explanations, such as residual confounding, where people living in high walkable neighbourhoods are different to people residing in low walkable neighbourhoods.

For ethical and practical reasons, randomisation is virtually impossible in research examining the impact of neighbourhood built environments on walking and physical activity.[24] Several alternative designs may be considered to extend the current evidence base built primarily on cross-sectional studies. For example, longitudinal analysis of people who remain in their neighbourhoods (eg, examination of environmental predictors of physical activity initiation/maintenance among 'non-movers'), longitudinal analysis of people who relocate to neighbourhoods with different environmental attributes (ie, relocation studies) and evaluations of environmental interventions are all longitudinal by nature, which allows for establishing the temporal sequence of cause and effect, a key criterion for causation. Further, these study designs are better at accounting for confounding than cross-sectional studies because they provide opportunities for comparing exposures and/or outcomes within an individual, instead of comparing people living in different types of neighbourhoods at one point in time. Still, these alternative designs have their advantages and limitations. For example, opportunistic evaluations of environmental interventions are less subject to self-selection bias (ie, people choose to live in neighbourhoods to accommodate their lifestyle preferences, such as their propensity for active travel[25]) compared with the other two longitudinal study designs discussed here. However, researchers do not have control over the timing, location and

nature of the intervention.[26] Neither do they have control over the dose of the intervention. As environmental change is usually slow and incremental,[27] it may not provide a sufficient 'dose' required for behavioural change during the time frame of the evaluation. In fact, some evaluations of environmental interventions on physical activity had mixed findings[14] possibly due to these challenges. In longitudinal studies of non-movers, one may expect little changes in the outcomes because behaviours tend to habituate over time. Relocation studies, on the other hand, follow the concept of 'mobility biographies', where stabilised behavioural patterns are 'interrupted' by life events, including environmental changes as a result of residential relocation.[28] Moreover, because environmental exposures pre-relocation and post-relocation can be quantified, changes in exposures can be evaluated as a 'natural experiment', and there have been calls for such designs to evaluate effects of neighbourhood environments on health behaviour and outcomes.[24 29 30] However, relocation studies are still subject to confounding, such as reasons and motivations for relocation.

In summary, evaluations of walking, physical activity and travel behaviour before and after people relocate between neighbourhoods that differ in environmental attributes offer a unique opportunity to examine the role of neighbourhood environments, not only within the context of residential relocation and mobility biographies, but also extend the current evidence on built environments and physical activity/travel behaviour in general by addressing some critical methodological limitations of cross-sectional studies. To the best of our knowledge, no other study has systematically reviewed the evidence on the effects of residential relocation on walking, physical activity or travel behaviour. In the present systematic review, we aim to synthesise the current evidence on the association between neighbourhood built environments and walking, physical activity and travel behaviour within the context of residential relocation.

METHODS

Data sources and searches

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42017077681, available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=77681). This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (online supplementary table 1).[31]

Systematic searches were conducted from database inception to March 2017, in the electronic databases MEDLINE, The Cochrane Library, EMBASE, CINAHL, SPORTDiscus, PsycINFO, Informit, Avery and RIBA for peer-reviewed papers, and The Grey Literature Report and ProQuest Dissertations and Theses Global for grey literature. Additional articles were identified through backward and forward citation tracking of included publications, and using the authors' own reference libraries. The list of search terms used in our MEDLINE search, which was adapted for searches in other databases, can be found in online supplementary table 2.

Eligibility criteria

A study was eligible for inclusion if it (1) measured changes in neighbourhood built environment attributes as a result of residential relocation (either prospectively or retrospectively); (2) included a measure of physical activity, walking, cycling or travel modal change as an outcome; (3) was quantitative and (4) included an English abstract or summary.

A study was excluded if it (1) was based on simulation data only[32]; (2) was conducted in the context of relocation on a university campus or at work[33]; (3) focused on international migration[34]; (4) examined social environments only[35] or (5) did not clearly define or measure the built environment attributes.[36 37] Specifically, exclusion criterion 3 was chosen because individuals and their environments may not be comparable pre-immigration and post-immigration. Exclusion criterion 5 applies to relocation studies where the environment was vaguely defined or not measured (eg, moving to a 'New Urbanist-inspired' development,[36] or a mixed-use development[37]) and therefore one cannot determine how built environment attributes changed after relocation.

Study selection

Following a standard protocol, two authors (BN and DD) independently screened studies for eligibility based on the title, abstract and full text. Uncertainty was discussed involving a third author (KG), and any disagreement was resolved by consensus. A PRISMA flow diagram presents the summary of the study selection process (figure 1).

Data extraction

Information about each paper was extracted by BN and DD independently for quality assurance. Any disagreement was discussed until consensus was reached.

At the study level, the following information was extracted: study name (if any), study design, setting and follow-up, sample recruitment, sample characteristics, neighbourhood environmental attributes (perceived or objectively measured), covariates, whether accounted for residential self-selection, potential moderators/effect modifiers tested and main findings.

At the result level, information about each finding was extracted based on the combination of environmental exposure and walking/physical activity/travel behaviour outcome. For studies that reported both cross-sectional and prospective longitudinal analyses,[38–42] we extracted findings from longitudinal and quasi-experimental analyses only because of the inability to ascertain changes in environmental attributes from cross-sectional analyses. Further, in addition to physical activity, walking and cycling outcomes, we also extracted results regarding public transport and car use[43 44] as these can serve as important secondary outcomes. This is because a modal change from driving to public transport use is relevant to an active lifestyle.[43 44] For studies that involve modal change,[40 45] it is important to present information on all transport modes to provide a complete picture. Finally, although our search protocol excluded studies that exclusively examined the neighbourhood social environment, we also extracted results regarding perceived safety and sociability[40–42 46 47] because both these attributes are closely linked to aspects of the built environment.[48 49]

Data synthesis

General characteristics about each selected study, including country, study name, study design, neighbourhood environment measures (objective and/or perceived), walking/physical activity/travel behaviour measure (objective or self-reported) and whether residential self-selection was accounted for, and if so, how, were summarised and tabulated.

Extracted study results were synthesised in separate tables for retrospective longitudinal and prospective longitudinal studies. Retrospective longitudinal studies (often referred to as quasi-longitudinal studies in the planning and transportation literature)

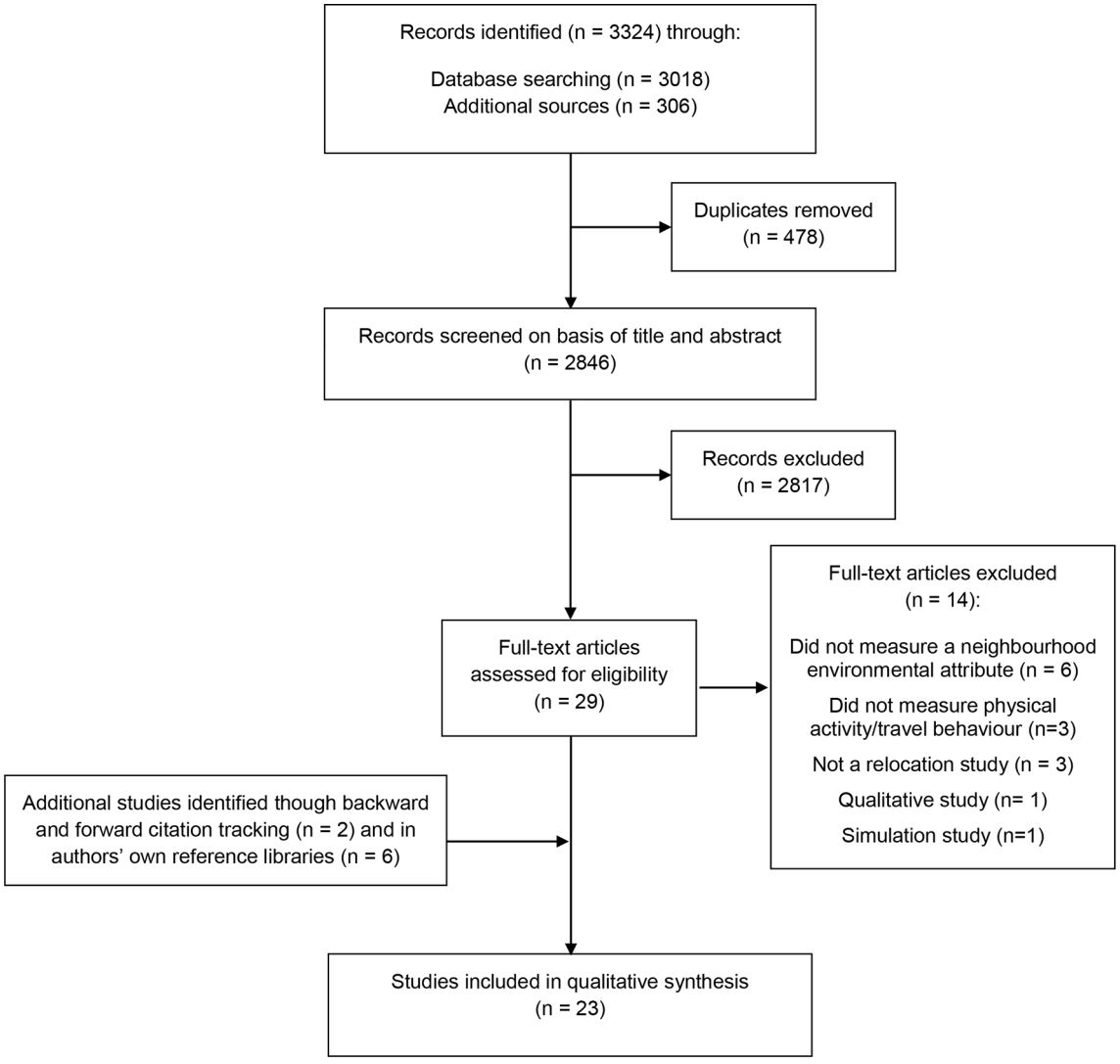

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

refer to a study design where participants retrospectively report for a defined time in the past (eg, 1 year ago, prior to relocation) and the present to determine the effects of a change in an attribute (eg, neighbourhood walkability) on behaviour (eg, walking).[40–42 47 50] Although this type of research design was named differently by some studies, such as a quasi-longitudinal pre–post design, for the purpose of this systematic review, we define them consistently as retrospective longitudinal studies. Longitudinal prospective studies include observational (cohort)[38] and natural experimental studies,[39 51] where naturally occurring events, such as moving to a new community, are evaluated as defined interventions in a prospective fashion.

For each study, all tested associations (unadjusted and adjusted) involving change in neighbourhood environmental attributes (exposures) and walking/physical activity/travel behaviour (outcomes) were considered. Because of the heterogeneity in the exposure and outcome measures, we could not quantitatively synthesise the effect sizes, instead, we grouped the results into categories and semiquantitatively summarised them based on the direction and significance of the associations. For environmental attributes, we developed a grouping scheme similar to that used in previous literature reviews,[52 53] where attributes were allocated to subcategories under 'recreation environment', 'neighbourhood design', 'transportation environment', 'aesthetics', 'crime-related safety', 'social environment' and 'aggregated characteristics'. For the outcomes, we categorised walking into recreational/leisure, transport and total walking; physical activity into recreational, transport and total physical activity; and other travel behaviour into cycling, public transport use and driving. We did not separate cycling for recreational and transport because only one study included some recreational cycling outcomes.[54] We developed a matrix to tabulate the extracted results using '+' to denote statistically significant ($P<0.05$, unless noted otherwise) associations in the *expected* direction, '–' to denote significant associations in the *unexpected* direction and '0' for non-significant associations.[52] The expected direction is based on the existing evidence base and the concept that activity friendly neighbourhood environments characterised by mixed land use and well-connected streets with good access to parks and recreation facilities, public and alternative transportation options, and low traffic and crime, are conducive to walking, physical activity and active travel, while discouraging car driving. Specifically, the expected direction for each association is presented in online supplementary table 3.

We allowed each study to contribute more than one finding to each combination of neighbourhood environmental attribute and outcome. When a study included different exposure measures for the same category of environmental attribute, we

Table 1 Characteristics of selected articles (n=23)

Characteristics	Studies (n)	References
Country		
Australia	5	46 51 54 55 58
Canada	2	63 65
China	1	66
Germany	3	28 45 64
UK	2	47 59
USA	10	27 38–42 50 60–62
Studies with single/multiple publications		
RESIDential Environment Project	5	46 51 54 55 58
A retrospective longitudinal study conducted in Northern California, USA	4	40–42 50
Single publication from a study	14	27 28 38 39 45–47 59–63 65 66
Study design		
Prospective longitudinal	15	27 28 38 39 45 46 51 54 55 58–63
Retrospective longitudinal	8	40–42 47 50 62 64–66
Neighbourhood environment measures		
Objective	11	27 38 39 59–66
Perceived	3	28 45 47
Both	9	40–42 46 50 51 54 55 58
Physical activity measures		
Objective	1	39
Reported	22	27 28 38 40–42 45–47 50 51 54 55 58–66 78
Accounted for self-selection		
Yes	13	27 39–42 46 47 50 51 55 58 64 65
Not mentioned	8	28 38 45 54 60–63

considered these as distinct findings. For example, Knuiman *et al* measured land use mix objectively using a Geographic Information System (GIS) within a 1600 m street network from participants' homes and participants' perceptions about the number of types of destinations within their neighbourhood.[55] In this case, both findings were counted as two separate associations. Similarly, when a study included multiple outcomes for the same environmental attribute that did not overlap, such as cycling for leisure and cycling for transport,[54] we considered them as distinct associations.

Given that studies present their results differently (eg, some present only the final models while others present unadjusted and different versions of adjusted models), to ensure that results from one study are not inflated as a result of duplication, we adopted the following protocols for assigning '+', '–' or '0' to each comparison. (1) When different models for the same association (using the same exposure and outcome) were presented, we determined the significance and direction of association based on the model that at least adjusted for demographic characteristics, socioeconomic status and neighbourhood self-selection. Alternatively, if the authors explicitly discussed that one model is less biased than the other, we then coded this association based on the less biased model. For example, Braun *et al* tested the association between a walkability index and walking outcomes using both random and fixed effects models.[27] They argued that estimates from random effects models were more biased because of residual self-selection bias; we therefore coded this association based on results from the fixed effects model. (2) When we could not select the least biased model based on criterion 1, we coded this association based on the consistency of results. For example, if at least 60% of the adjusted results were significant in the expected direction, we coded this result as '+', if the pattern of the results was inconsistent (eg, 50% '+', 50% '0'), we coded it as '?' to denote the uncertainty of the association.

Finally, we summarised results regarding each environmental attribute across different outcome measures by calculating a consistency score as the percentage of total associations being significant in the expected direction.[52] Two consistency scores were developed. The first one refers to the number of associations coded '+' as a proportion of the total number of associations, which denotes the overall consistency of an environmental attribute with different outcomes at the level of associations (findings). Using the same scoring system, we summarised results about environmental attributes across different outcomes and each outcome across different environmental attributes. Due to the small number of studies overall, particularly regarding domain-specific walking and physical activity, we combined different subcategories of walking and physical activity within the larger categories.

The second score applied weights to associations reported from the same study (in the same or different publication), so that the overall consistency of associations was not driven by single studies. Specifically, we applied a weighting scheme similar to that reported in a systematic review by Cerin *et al*.[16] For example, Handy *et al* reported associations between three land use mix indicators and overall walking,[41] and Cao *et al* reported two[50]; given that the two publications were based on the same study, we assigned each of the five findings a weighting of 0.2. Applying weighting, the second summary statistic indicates the overall consistency of an environmental attribute with different outcomes at the study level.

Quality appraisal and risk of bias analysis

We developed a quality appraisal checklist (online supplementary table 4) based on previous systematic reviews[16 56] with additional items designed particularly for relocation studies (eg, 'Did the study assess whether the participants experienced life changing events which may have led them to relocate and did they account for these events?'). Two authors (BN, KG) independently performed quality appraisal, and any disagreement was resolved by consensus.

We conducted the following three risk of bias analyses for the data synthesis by recalculating the consistency scores after (1) excluding all studies with low-quality scores (<5) based on quality appraisal, (2) excluding all studies that did not adjust for self-selection bias (see online supplementary table 5 for details) and (3) limiting to findings involving objectively measured neighbourhood environmental attributes. These risk of bias analyses aim to examine how sensitive study findings are to the quality of the included studies, self-selection bias and the measurement mode of the neighbourhood environment. Previous studies suggest attenuated associations after accounting for self-selection and considerably different levels of consistency in associations by the measurement mode of neighbourhood environmental attributes.[57]

RESULTS

Selection of studies

The database searches yielded 3324 records (figure 1). After removing duplicates, 2846 records remained. After excluding 2817 records based on reading the titles and abstracts, the full texts of the remaining 29 were examined and an additional

Table 2 Summary of results from retrospective longitudinal studies (n=8)

	Walking*	Physical activity*		Other travel behaviour			Consistency score†	
	Transport	Recreation	Total	Cycling	Public transport	Driving	Unweighted +%	Weighted +%
Recreation environment								
Parks/green space/recreation facilities	Aditjandra *et al*,[47] (+)						1/1 (100%)	1/1 (100%)
Neighbourhood design								
Land use mix/destinations	McCormack (+)		McCormack (**0**)	McCormack (**0**)			1/3 (33%)	1/3 (33%)
Transportation environment								
Overall transportation access‡	Aditjandra *et al*,[47] (+); Cao *et al*,[50] (+); Handy *et al*,[40] (+); Handy *et al*,[41] (+)	Handy *et al*,[42] (+)		Handy et al,[41] (+)	Aditjandra *et al*,[47] (+)	Cervero and Day,[66] (**0**,–)§; Handy et al,[40] (0)	7/10 (70%)	5/7 (71%)
Aesthetics	Aditjandra *et al*,[47] (+); Handy *et al*,[40] (+); Handy et al,[41] (+)	Handy *et al*,[42] (+)				Handy *et al*,[40] (0)	4/5 (80%)	3/4 (75%)
Crime-related safety	Aditjandra *et al*,[47] (+); Cao *et al*,[50] (+); Handy*et al*,[40](+); Handy et al,[41] (+)	Handy *et al*,[42] (+)				Handy *et al*,[40] (+)	6/6 (100%)	4/4 (100%)
Social environment	Aditjandra *et al*,[47] (0); Cao *et al*,[50] (+); Handy *et al*,[40] (+); Handy *et al*,[41] (+)	Handy *et al*,[42] (0)		Handy *et al*,[41] (+)		Handy *et al*,[40] (0)	4/7 (57%)	2/4 (50%)
Aggregated characteristics								
Sprawl				Klinger and Lanzendorf,[64] (**0**)	Klinger and Lanzendorf,[64] (**0**)	Klinger and Lanzendorf, (**0**)[64]	0/3 (0%)	0/3 (0%)
Overall accessibility (to destinations and transportation)	Handy *et al*,[40] (+); Handy*et al*,[41] (+)				Aditjandra *et al*,[47] (+)¶	Handy *et al*,[40] (+)	4/7 (57%)	3/6 (50%)
Consistency score†								
Unweighted +%	18/19 (95%)	3/5 (60%)		2/4 (50%)	2/3 (67%)	2/8 (25%)		
Weighted +%	10/11 (91%)	3/5 (60%)		2/4 (50%)	2/3 (67%)	2/7 (29%)		

Bold entries denote objectively measured environmental attributes.
*The columns for recreation walking and transport physical activity were omitted because no study examined these outcomes.
†Unweighted consistency score: the percentage of associations coded '+' out of the total number of associations; weighted consistency score: applied weighting to results from the same study by a factor of 1/total number of results from the same study in one cell. For this table, data from refs.[40–42 50] were from the same study.
‡Overall transportation access: access to a range of specific or non-specific transportation options, such as sidewalks, bike paths, public transport and roads.
§A study can contribute to more than one finding to each combination of built environment attribute and outcome when it involved different exposure measures for the same category of environmental attribute or different measures for the same domain of outcomes.
¶Indirect effects mediated by car ownership.
+, statistically significant associations in the expected direction; –, statistically significant associations in the unexpected direction; 0, non-significant associations (expected direction is detailed in online supplementary table 2).

14 full texts were excluded. With an additional 2 studies identified through backward and forward citation tracking, and 6 from the authors' own reference libraries, a total of 23 publications were appraised and synthesised.

Study characteristics

Fifteen of the publications were based on longitudinal prospective studies[27 28 38 39 45 46 51 54 55 58–63] and eight based on retrospective longitudinal/quasi-longitudinal studies.[40–42 47 50 64–66] Altogether, the publications were based on studies conducted in six countries (table 1), with the USA (n=10) and Australia (n=5) contributing to most of the publications. Five publications were based on the RESIDential Environment Project (RESIDE) in Perth, Australia, and four were based on a study conducted in Northern California, USA. In terms of the measurement of neighbourhood environmental attributes, 11 reported objective measures only, mostly based on a GIS, 3 included perceived measures and 9 included both objective and perceived environmental measures. All but one study[39] relied on self-reported measures of walking/physical activity/travel behaviour. More than half of the publications reported some measures of residential preferences to account for self-selection bias. Details about each study, including relevant findings, are presented in online supplementary table 5. Overall, the quality scores varied, ranging from 1 to 7 on a scale from 0 to 9, with 10 of the 23 studies scoring five or more points. Longitudinal prospective studies scored much higher (range: 2–7, mean: 5) than retrospective longitudinal studies (range: 1–3, mean: 2.6). The results of the critical appraisal are presented in online supplementary table 6.

Summary of findings from retrospective longitudinal studies

As shown in table 2, overall transportation access, social environment, crime-related safety and accessibility were among the most assessed environmental attributes and walking was the most commonly used outcome. Overall, there was consistent support for the effects of change in neighbourhood environmental attributes through residential relocation on the change in a range of outcomes, particularly walking, where the consistency scores were >90%. Most environmental attributes yielded a consistency score of ≥50% across outcomes and the score was particularly high for overall transportation access (access to a range of specific or non-specific transportation options, such as sidewalks, bike paths, public transport and roads), aesthetics and crime-related safety. After accounting for multiple findings from the same study, the weighted consistency scores were slightly lower than the unweighted ones. It is important to note that given the small number of retrospective longitudinal studies many of the environmental attribute–outcome combinations were not examined, and most of those that were examined involved a small number of studies.

Summary of findings from longitudinal prospective studies

Given the larger number of longitudinal prospective studies, a broader range of environmental attribute–outcome combinations were explored (table 3). The most examined environmental attributes were land use mix/destinations and public transport access/services and the most commonly used outcomes were transport walking and cycling. Compared with results from retrospective longitudinal studies, those from prospective longitudinal studies were much less consistent. Among all environmental attributes, walkability/pedestrian friendliness had the highest weighted and unweighted consistency scores, although the findings only involved three studies. Most environmental attributes had consistency scores of 25%–40%, providing less consistent evidence for the effects of change in neighbourhood environments through residential relocation on change in walking/physical activity/travel behaviour. A few attributes had a consistency score of 0%, including traffic, aesthetics, neighbourhood type, sprawl, all of which were based on a small number of studies. Across outcomes, associations involving a walking outcome had the highest consistency scores while those involving physical activity and cycling had much lower scores.

Risk of bias analysis

Three risk of bias analyses were conducted separately for retrospective longitudinal and prospective longitudinal studies (online supplementary table 7). First, when excluding studies with a quality score of ≤4, 0 retrospective longitudinal and 10 prospective longitudinal studies remained. The consistency scores were very similar in the risk of bias analyses, and in some cases slightly higher, among the higher-quality studies compared with all studies. Second, when limiting to studies that accounted for self-selection, the consistency scores from retrospective longitudinal studies remained nearly identical while those from longitudinal prospective studies slightly fluctuated, though the overall level of consistency remained similar. Finally, when limiting to findings involving objectively measured neighbourhood environmental attributes, consistency scores remained similar or slightly lower in retrospective longitudinal studies and similar (or in some cases slightly higher) in longitudinal prospective studies. Overall, results from risk of bias analyses showed robustness in our findings, but are somewhat limited by the small numbers of studies/findings after exclusion.

DISCUSSION

To our knowledge, this is the first systematic review that synthesises the evidence on the effects of change in neighbourhood environments through residential relocation on walking, physical activity and travel behaviour. Given the potential for walking to increase total physical activity levels and health, efforts to implement environment-changing interventions seem logical and may have an impact at the population level. Our review found a scarcity of literature on residential relocation, with only 23 publications from 16 studies in six countries (five high-income countries and one upper-middle-income country) meeting our inclusion criteria. Overall, the studies are heterogeneous in terms of design and measures, making it difficult to draw conclusions about specific associations. Summarised across different exposure and outcome measures, the overwhelming pattern of associations suggests a much stronger evidence for the effects of change in neighbourhood environment through residential relocation in retrospective longitudinal (quasi-longitudinal) than prospective longitudinal studies; and for both study designs, the most consistently significant associations involved walking as an outcome.

The differences in findings between prospective longitudinal and retrospective longitudinal studies highlight the importance of research design. In principle, although prospective longitudinal studies are not perfect, a retrospective longitudinal/quasi-longitudinal design is more subject to bias, with participants more prone to recall and social desirability biases (ie, they report in favour of an improvement).[40 42] In cases where individuals were prompted to report the change in both neighbourhood environment and physical activity/travel behaviour,[47 50] common source bias may be an additional concern. Previous literature has also documented the 'honeymoon effect' where recent movers are likely to rate their new neighbourhood more favourably.[67] The common source bias and honeymoon effect combined may particularly bias the associations away from null among those who recently relocated compared with those who relocated further in the past, or the control group who did not relocate. Taking these potential biases into consideration, the high consistency in findings from retrospective longitudinal studies should be interpreted with caution.

The small number of studies on residential relocation is in contrast to the vast and ever-growing body of literature on built environments and physical activity in general.[16 68] To contextualise our review, we have summarised all literature reviews on built environments and physical activity among adults that we identified through previous reviews of reviews[24 68] and we updated this list through systematically searching literature databases (see table 4 and online supplementary table 8 for unabridged information). Nearly 30 reviews have been published, with some reviews including a large number of empirical studies,[15 16 69] indicating the popularity of the field. However, the current evidence base predominantly relies on cross-sectional studies, and some literature reviews have even excluded longitudinal or experimental studies a priori to solely focus on cross-sectional studies.[70–74] While cross-sectional studies are important for generating hypotheses at an early stage of scientific field development, and have contributed to understanding the plausibility, consistency and the specificity of the associations between the built environment and physical activity,[53] they are inherently subject to ambiguity in temporality, residual confounding and self-selection bias. Given that the ultimate goal of research on built environments and physical activity is to inform urban planning, transportation and public health policy and practice, we must consider evidence that is based on

Table 3 Summary of results from longitudinal prospective studies (n=15)

	Walking			Physical activity		Other travel behaviour			Consistency score*	
	Recreation	Transport	Overall	Transport	Total	Cycling	Public transport	Driving	Unweighted +%	Weighted +%
Recreation environment										
Parks/green space/recreation facilities	Giles-Corti (**0**)					Beenackers *et al*,[54] (+,+,0,0)†			2/5 (40%)	0.5/2 (25%)
Neighbourhood design										
Residential/population density	Coogan *et al*,[60] (?)	Coogan *et al*,[60] (+); Knuiman *et al*,[55] (**0**, 0)†		Clark *et al*,[59] (**0**)		Beenackers *et al*,[54] (**+,0**)†		Clark *et al*,[59] (**0**)	2/8 (25%)	1.5/6 (25%)
Street connectivity		Knuiman *et al*,[55] (+, 0)†	Wells and Yang,[39] (+)			Beenackers *et al*,[54] (**0,+**,0,0,0)†			3/8 (38%)	1.7/3 (57%)
Land use mix/destinations	Hirsch (**0**)	Giles-Corti (+); Hirsch *et al*,[61] (+); Knuiman *et al*,[55] (**+,+,+,+**)† Scheiner and Holz-Rau,[28] (+); Scheiner and Holz-Rau,[45](+); Wasfi (**+,+,0**)†	Wells and Yang,[39] (-)	Clark *et al*,[59] (**+,0,0**)†		Beenackers *et al*,[54] (?, 0,**0**)† Scheiner and Holz-Rau,[28] (0); Scheiner and Holz-Rau,[45] (0)	Scheiner and Holz-Rau,[28] (0)	Clark *et al*,[59] (**0,0,0**)† Scheiner and Holz-Rau,[28] (0);	11/26 (42%)	5/14 (36%)
Transportation environment										
Walking/cycling facilities						Beenackers *et al*,[54] (+,0,0)†			1/3 (33%)	1/3 (33%)
Public transport access and services		Knuiman *et al*,[55] (**+,+,+,+**)† Scheiner and Holz-Rau,[28] (0,0,0);†		Clark et al,[59] (**0,0**)†		Scheinerand Holz-Rau,[28] (0,0,0)†	Scheiner and Holz-Rau,[28] (0,0,0);† Scheiner and Holz-Rau,[45] (+)	Clark et al,[59] (**0,0**)† Scheiner and Holz-Rau,[28] (0,0,0);† Scheiner and Holz-Rau,[45] (+)	6/22 (27%)	3/9 (33%)
Parking		Scheiner and Holz-Rau,[28] (0)				Beenackers *et al*,[54] (0) Scheiner and Holz Rau,[28] (0)	Scheiner and Holz-Rau,[28] (+)	Scheiner and Holz-Rau,[28] (+)	2/5 (40%)	2/5 (40%)
Traffic						Beenackers *et al*,[54] (0)			0/1 (0%)	0/1 (0%)
Aesthetics						Beenackers *et al*,[54] (0,0)†			0/2 (0%)	0/1 (0%)
Crime-related safety	Foster *et al*,[46] (**0**,+)†	Foster *et al*,[46] (**0**,+)†	Foster *et al*,[46] (**0**,+)†			Beenackers *et al*,[54] (0)			3/7 (43%)	1.5/4 (38%)
Aggregated characteristics										
Walkability/pedestrian friendliness	Giles-Corti (+)	Giles-Corti (+)	Braun *et al*,[27] (**0**)					Krizek (+,+)†	4/5 (80%)	3/4 (75%)
Neighbourhood type (New-Urbanist, traditional)	Christian *et al*,[58] (0)	Christian *et al*,[58] (0)	Christian *et al*,[58] (0)						0/3 (0%)	0/3 (0%)
Sprawl			Lee (**0**)		Lee (**0**)				0/2 (0%)	0/2 (0%)
Consistency score*										
Unweighted +%	22/42 (52%)			1/7 (14%)		5/28 (18%)	2/6 (33%)	4/14 (29%)		
Weighted +%	10.7/26 (41%)			0.3/4 (8%)		1.5/12 (12%)	2/4 (50%)	3/8 (38%)		

Bold entries denote objectively measured environmental attributes.
*Unweighted consistency score: the percentage of associations coded '+' out of the total number of associations; weighted consistency score: applied weighting to results from the same study by a factor of 1/total number of results from the same study in one cell. For this table, data from refs.[46 51 54 55 58] were from the same study.
†A study can contribute to more than one finding to each combination of built environment attribute and outcome when it involved different exposure measures for the same category of environmental attribute or different measures for the same domain of outcomes.
+, statistically significant associations in the expected direction; –, statistically significant associations in the unexpected direction; 0, non-significant associations (expected direction is detailed in online supplementary table 2; ?, inconsistent results within an association between an environmental attribute and an outcome. In the case of,Coogan *et al*, [60] an increase in housing density was significantly associated with both increase and decrease in exercise (recreational) walking; in Beenackers *et al*, [54] 'access to a mixed service' had inconsistent associations with taking up cycling for transport (50%) in adjusted models.

Table 4 Summary of existing literature reviews* on built environments and physical activity/travel behaviour among adults (n=28)

First author (year)	Included articles (search period), n	Design of included studies	Scope of study	Main findings
Arango (2013)	15 (1990 to August 2012)	All CS	To review the association between perceived environments and adult PA in Latin America	Most associations were non-significant. Strongest evidence for leisure-time PA with day safety and transport PA with street lighting presence.
Bancroft (2015)	20 (1990 to June 2013)	17 CS, 3 PL	To review the association between park access and objectively measured PA in the USA (all ages)	Associations varied between studies. Reported park characteristics and smaller buffer sizes more predictive of PA.
Barnett (2017)	100 (2000 to September 2016)	95 CS, 5 PL, 1 QE	(1) To review and meta-analyse the association between BE attributes, PA and/or walking (older adults); (2) To examine potential moderators	Associations differ by BE attributes and PA measures. Strongest evidence for: walkability, safety from crime, access to destinations, recreational facilities and parks/public open space. No consistent moderators.
Butler (2011)	29 (2005 to December 2009)	All CS	To review PA studies which included one or more GIS measure of the BE	Increase in studies using PA-relevant GIS BE measure, but lack of standardisation among BE; difficult to synthesise evidence
Casagrande (2009)	10 (1966 to July 2007)	All CS	Review of BE association with PA, diet and obesity among adult African-Americans	All BE PA studies (n=7) measured perceptions of BE. Safety from crime had the strongest association with PA among urban dwellers (not consistent across studies). Light traffic and the presence of sidewalks were positively but inconsistently associated with meeting PA recommendations in metro and non-metro areas.
Cerin (2017)	42 (2000 to September 2016)	All CS	Review and meta-analysis of BE associations with active travel in older adults (aged ≥65 years)	Strong links between neighbourhood BE and active travel. Sufficient evidence for positive associations between total walking for transport and residential density/urbanisation, walkability, street connectivity, overall access to destinations/services, land use mix, pedestrian friendly features and access to several types of destinations.
Cunningham (2004)	27 (1966 to 2002)	All CS	To identify theoretical models and key concepts used to predict the association between BE and seniors' PA	Limited # of studies focused on seniors (n=6). Range of theoretical models and BE measurement methods. Positive relationships for: PA, safety and aesthetics; findings mixed for PA associations with sidewalks or convenience of facilities.
Ewing (2010)	62 (up to 2009)	Not described	A meta-analysis of the associations between BE and travel (VMT, walking, transit)	Travel variables are generally inelastic with respect to change in measures of the BE. Walk trips are most strongly associated with the design and diversity dimensions of BEs.
Ferdinand (2013)	169 (1990 to April 2011)	All observtnl	Review relationship between BE and PA or obesity rates (all ages)	89.2% of studies found a beneficial relationship between BE and PA. Studies using objective (vs self-report or other) PA measures were 18% less likely to identify a beneficial relationship.
Foster (2008)	41 (up to July 2007)	All CS	(1) To summarise the individual, social and BE characteristics that are associated with perceived safety; (2) to examine the association between real and perceived crime-related safety, and between factors known to influence crime-related safety and PA	Perceived safety tends to affect the PA of groups already known to exhibit greater anxiety about crime (women, elderly). BE PA findings inconsistent, likely due to measurement limitations. More specific measures warranted.
Fraser (2011)	21 (up to June 2009)	8 CS, 7 surveys with exptl measures, 2 RL, 2 ecological, 1 pre–post, 1 qual	To review observtnl and exptl studies examining association between objectively measured BE and cycling behaviour (all ages)	No studies rated strong on study quality and none from low-income/middle-income countries. Significant positive findings for objective BE measures and higher rates/frequency of cycling in 11 studies, including cycle routes, Safe Routes to School initiatives, proximity of destinations, separation from traffic, population density, proximity of cycle paths and presence of green space/recreational land. Significant findings with cycling: traffic danger, sloping terrain and long trip distance. 10 studies found no positive association between BE and cycling.
Frost (2010)	20 (up to June 2008)	19 CS, 1 PL	To review the association between BE and PA in adults in rural settings	Positive associations found among pleasant aesthetics, trails, safety/crime, parks and walkable destinations. Measures of PA varied.
Grasser (2013)	34 (up to August 2010)	33 CS, 1 PL	To review objectively measured walkability and active transport and weight-related outcomes in adults	BE measures consistently associated with walking for transport: gross population density, intersection density and walkability indexes. Inconsistent results on weight-related measures.

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Table 4 Continued

First author (year)	Included articles (search period), n	Design of included studies	Scope of study	Main findings
Heath (2006)	3 separate reviews (see scope)	CS QE time series	To review studies addressing environmental and policy strategies to promote PA: (1) community scale urban design and land use (n=12, 1993–2003); (2) street-scale urban design and land use (n=6, 1987–2003); (3) transportation and travel (n=1, 1990–1998)	Two interventions were effective in promoting PA (community-scale and street-scale urban design and land use policies and practices). Evidence is insufficient to assess transportation policy and practices to promote PA.
Humpel (2002)	19 (up to 2002)	18 CS, 1 PL	To review the relationships between BE attributes and PA behaviours in adults	Self-report BE studies more frequent than studies incorporating objective BE. Variables representing access to facilities and specific opportunities for PA, and aesthetics were associated with PA.
Kaczynski (2007)	50 (1998 to December 2005)	All CS	To review what types of PRSs are most related to PA and how proximity to PRSs is related to PA (all ages)	Diverse operationalisations of both parks or recreation and PA were employed (eg, proximity definitions) as were a range of PA variables. Mixed associations were observed for different types of PRSs, with parks, trails and other open spaces (eg, golf courses) having more consistent positive relationships. Proximity to PRSs were generally found to be associated with increased PA.
Kaczynski (2008)	50 (1998 to December 2005)	All CS	To review what types of PRSs are most related to PA and how PRSs were related to different functions and intensities of PA (all ages)	PRSs were more likely to be positively associated with PA for exercise or utilitarian functions than for recreational PA. PRSs were commonly associated with walking; mixed results with moderate and vigorous PA.
Mayne (2015)	37 (January 2005 to January 2014)	13 natural expts, 24 QE	A review of studies in the medical literature relating to natural or QE in obesity research (all ages)	PA studies (n=17) generally found stronger impacts when the intervention improved infrastructure for active transport or had a longer follow-up period (>6 months).
McCormack (2004)	12 (2000 to 2004)	All CS	A review of associations between BE and PA among adults incorporating self-report and objective measures of BE and PA	Positive associations between both perceived and objectively measured BE and PA. Availability, access and convenience of destinations, neighbourhood functionality and aesthetics were associated with PA. Lack of association between specific types of PA and specific setting in which it is performed.
McCormack (2011)	33 (1996 to 2010)	20 CS, 13 QE	To review the relationship between objective measures of BE and PA among adults for studies attempting to control for neighbourhood self-selection	BE PA associations were either in the expected direction or null. Land use mix, connectivity, population density and overall neighbourhood design were important PA determinants. BE more likely to be associated with transport-related walking than other types of PA. Self-selection adjustment attenuated relationships.
Moran (2014)	31 (1996 to2012)	All qual	To review qualitative studies of BE and PA in older adults	Studies combined interviews with spatial qualitative methods that added depth to understanding of BE PA relationships. Themes identified: pedestrian infrastructure, safety, access to facilities, aesthetics and environmental conditions.
Ogilvie (2004)	22 (up to end of 2002)	3 RCTs, 7 non-rand cont PL, 11 uncontrolled PL, 1 cont RL	To review the effects of population level interventions to promote a shift from using cars towards walking and cycling	Engineering measures were not found to be effective in a modal shift from cars to walking and cycling.
Owen (2004)	18 (up to 2004)	16 CS, 2 PL	To review association between objective and perceived environment and walking	Aesthetics, convenience of walking facilities, accessibility, level of traffic and composite BE measures were associated with walking for different purposes. Attributes associated with walking for exercise different from those associated with walking to get to/from places.
Pucher (2010)	139 (1990 to 2010)	CS, PL (#s not provided)	To review interventions targeting increased levels of cycling	Findings suggested positive impacts of interventions, but increases in cycling are generally small. Large variation in estimated impacts by type of intervention and study design, location and timing. Most studies limited due to study design adopted.

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Table 4 Continued

First author (year)	Included articles (search period), n	Design of included studies	Scope of study	Main findings
Saelens (2003)	14 (up to 2003)	All QE/CS	Review of transport, urban design and planning literature to determine associations between BE variables and transport walking and cycling	Higher density, greater connectivity and more land use mix is associated with higher rates of walking and cycling for transport. Transport, urban design and planning fields can contribute to multidisciplinary research on environmental contributions to PA levels in the population.
Saelens (2008)	13 reviews (2002 to 2006) and 29 studies (2005 to May 2006)	CS	To review the evidence of BE correlates of walking	Previous reviews and newer studies document positive associations of walking for transport with density, distance to destinations and land use mix. Associations between network connectivity, parks and open space and personal safety and transport walking are mixed. Relationships with recreational walking are less clear.
van Cauwenberg (2011)	31 (2000 to March 2010)	28 CS, 3 LP	To review the association between BE and PA in older adults	Results were inconsistent with most of the BE characteristics reporting non-significant relationships with PA, possibly reflecting limited number of studies and methodological issues.
van Holle (2012)	70 (January 2000 to August 2011)	69 CS, 1 LP	To review European specific studies on the relationship between BE and PA domains in adults	Convincing evidence on positive relationships with several PA domains: walkability, access to destinations and composite factor environmental quality. Transport PA more consistently related to BE. Lack of association with domain specific PA and access to recreation facilities, aesthetics, crime and traffic-related safety.

*The reviews were selected from previous reviews of reviews,[67 68] and an updated literature search using the same methodology outlined in this paper.
–, negative; BE, built environment; cont, controlled; CS, cross-sectional; expts, experiments; exptl, experimental; GIS, Geographic Information System; observtnl, observational; PA, physical activity; PL, prospective longitudinal; PRSs, parks and recreational settings; qual, qualitative; quant, quantitative; QE, quasi-experimental or quasi-experiments; rand, randomised; RCT, randomised controlled trial; RL, retrospective longitudinal; ,VMT, vehicle miles travelled.

stronger research designs, including, but not limited to, residential relocation studies.

Residential relocation: opportunities and challenges

Residential relocation provides a unique opportunity for improving the evidence base. One of the key limitations of cross-sectional studies is that those living in high and low walkability neighbourhoods may be substantially different (eg, socioeconomic status, propensity to be physically active), which violates the 'exchangeability' assumption for causal inference, and statistical methods cannot ensure total control of confounding.[75] Longitudinal studies (including residential relocation studies), on the other hand, compare an outcome within the individual. When time-varying variables are accounted for, a participant could serve as her/his own control,[60] which better accounts for residual confounding. Furthermore, studies on 'mobility biographies' argue that individuals are likely to be 'open-minded' to changing habitual travel behaviour and to resynchronise their behaviour with their new environment after relocation.[28 64] The implication is that residential relocation not only provides an opportunity for understanding the impacts of neighbourhood environments on behaviour during a period susceptible to behavioural change, but also serves as an ideal window of opportunity for interventions. For example, recently relocated residents should be made aware of the local facilities and opportunities for active living, as previous evidence suggests a mismatch between perceived and objectively measured neighbourhood environment and that perceived environmental attributes may be more strongly associated with physical activity than objectively measured neighbourhood attributes.[76]

However, as demonstrated by the overall low-quality score in our quality appraisal, relocation studies have methodological challenges. First and foremost, endogeneity of neighbourhood selection biases the estimate of associations between the built environment and physical activity in observational studies. Relocation studies, whether prospective longitudinal or retrospective longitudinal, are still subject to the same self-selection bias where individuals who are predisposed to lifestyle change (eg, those who are environmentally concerned) select their new residential neighbourhood to facilitate the change. Such unmeasured preferences or constraints that impact both neighbourhood selection and physical activity will lead to erroneous associations between neighbourhood environments and physical activity. Compared with cross-sectional studies, longitudinal studies (including relocation studies) provide the opportunity for establishing the temporality of residential preferences, exposures to neighbourhood environments and changes in travel behaviour/physical activity.[42] Such study designs paired with appropriate methods for accounting for self-selection bias, as outlined by Cao *et al*,[25] could potentially provide stronger evidence towards causality. Second, a unique challenge to relocation studies is confounding by concurrent life events that cause or accompany relocation and neighbourhood reselection. For example, people relocate in response to other life events, such as changing jobs, employment status or household size. Previous studies found that residential relocation was no longer associated with travel modal change when adjusted for other life events, such as birth of the first child and changing employer.[28 77] Therefore, it is important to account for major life events when assessing the association between relocation and walking/physical activity/travel modal change. Of all the studies in this review, less than half (n=9, 39%) explicitly adjusted for life events. Third, previous evaluations of environmental interventions suggest that significant behavioural change may be more likely to occur over a longer follow-up period,[14 78] possibly due to a 'lag time' to adapt to a new environment. Therefore, residential relocation studies need to be planned with longer-term follow-up in mind. Fourth, residential relocation

studies, along with other longitudinal studies, are subject to loss to follow-up. For example, most of the longitudinal studies reviewed had a drop-out rate of >30%. Therefore, appropriate handling of missing data is critical to prospective evaluations of residential relocation studies. Fifth, as researchers cannot influence the relocation process, studies involving residential relocation may encounter practical challenges. For example, some participants may have moved prior to the pre-move data collection leading to a smaller sample size than envisaged and a loss of power,[39] or due to unforeseen circumstances, pre-move data had to be collected retrospectively rather than prospectively as initially planned.[37] Such unexpected and uncontrollable events challenge the researchers to react promptly and pragmatically with the minimal compromise of research quality. Finally, in relocation studies, behaviour change is catalysed by relocation. It is unknown whether similar changes in environmental attributes will lead to changes in outcomes among non-movers. Hence, it is important to supplement evidence from relocation studies with longitudinal studies of non-movers and evaluations of environmental interventions.

Strengths and limitations

One of the strengths of this systematic review is that it adheres to the PRISMA statement for systematic reviews,[31] which is not standard practice in the field of built environments and physical activity/travel behaviour.[24] In addition, we developed methodologies to account for multiple publications of the same study along with several risk of bias analyses to determine how sensitive our overall findings are to specific studies, measurements, study design and quality. Our review is limited by the small number of studies, the relatively low quality of most studies, heterogeneous exposure and outcome measures, and not being able to take into account effect sizes in our synthesis. Finally, summarising across diverse environmental attributes and outcomes is methodologically challenging. While synthesising evidence by categorising these measures provides a 'big picture' perspective of the evidence, it also inevitably introduces biases in interpretation when lumping measures together.

What is already known?

- Attributes of neighbourhood built environments are associated with walking and physical activity based on a large body of literature that mainly consists of cross-sectional studies.
- Cross-sectional studies are particularly subject to biases and cannot provide the strongest and most policy-relevant evidence.
- In studies of neighbourhood environments, randomisation is virtually impossible, 'natural experiments' that evaluate effects of neighbourhood environments on health behaviour and outcomes provide opportunities for high-quality evidence.
- A number of studies examined the effects of environmental changes through residential relocation on walking, physical activity and travel behaviour. However, the evidence has not been synthesised or appraised.

What are the new findings?

- There is a paucity of relocation studies examining effects of built environments on physical activity/travel behaviour.
- The quality of the studies varied, with prospective longitudinal studies rating higher than retrospective longitudinal studies.
- There was encouraging evidence for the relationship between residential relocation and walking from retrospective longitudinal studies, but much weaker evidence from prospective longitudinal relocation studies.
- Future studies could benefit from using longitudinal data, such as travel panels and cohort studies, evaluating relocation effects over longer follow-up periods and accounting for self-selection and concurrent life events.

CONCLUSIONS

Overall, we found a paucity of studies on the associations between changes in neighbourhood built environment and walking/physical activity/travel behaviour outcomes in the context of residential relocation. The findings of these studies differ dramatically by study design, with retrospective longitudinal/quasi-longitudinal studies supporting a significant association whereas findings from prospective longitudinal studies were less consistent, but possibly also less biased. Further research should focus more on well-designed 'natural experiments'. Residential relocation provides a unique opportunity for studying environment-induced changes in physical activity. The literature reviewed here represents steps towards incremental improvement in quality evidence to inform policy and practice regarding urban design and transportation planning. However, the inadequate evidence base limits specific policy recommendations regarding how changes in a particular environmental feature or infrastructure will 'cause' health-promoting change in residents' physical activity and travel behaviour. Continuous improvement of the research evidence is critical to the field. Future studies could benefit from using longitudinal data sources, such as travel panels[45] and cohort studies,[38] evaluating relocation effects over longer follow-up periods and apply appropriate research designs and statistical approaches to account for self-selection and concurrent life events. Additional data from geographically diverse areas, particularly from low-income and middle-income countries, could also add to the current literature. In summary, this review appraises environmental changes for walking, physical activity and travel behaviour in a methodologically sound manner, aiming to refocus the research agenda of the built environment beyond cross-sectional studies to provide higher-quality evidence.

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