LONGITUDINAL RELATIONSHIPS OF THE NEIGHBOURHOOD BUILT ENVIRONMENT WITH CARDIO-METABOLIC HEALTH

Submitted by

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DECLARATION

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

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PUBLICATIONS, CONFERENCES, AND AWARDS

Publications during the candidature

1. **Chandrabose M**, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, Giles-Corti B, Sugiyama T. Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. Obes Rev. (2019);20(1):41-54.
2. **Chandrabose M**, Owen N, Giles-Corti B, Turrell G, Carver A, Sugiyama T. Urban Densification and 12-Year Changes in Cardiovascular Risk Markers. J Am Heart Assoc. 2019;8(15): e013199.
3. **Chandrabose M**, Cerin E, Mavoa S, Dunston D, Carver A, Turrell G, Owen N, Giles-Corti B, Sugiyama T. Neighborhood walkability and 12-year changes in cardio-metabolic risk: the mediating role of physical activity. Int J Behav Nutr Phys Act. 2019;16(1):86.

Conference presentations during the candidature

1. **Chandrabose M**, Owen N, Giles-Corti B., Turrell G, Carver A, Sugiyama T. *Urban densification and cardiovascular risk among Australian adults*. Oral presentation, Asian-Pacific Congress of Hypertension (**APCH**), November 2019, Brisbane, Australia
2. **Chandrabose M**, Cerin E, Mavoa S, Dunstan D, Carver A, Turrell G, Owen N, Giles-Corti B, Sugiyama T. *Neighborhood walkability and 12-year changes in cardio-metabolic risk: the mediating role of physical activity.* Poster presentation, International Society of Behavioral Nutrition and Physical Activity (**ISBNPA**) Annual Meeting, June 2019, Prague, Czech Republic
3. **Chandrabose M**, Owen N, Giles-Corti B., Turrell G, Carver A, Sugiyama T. *Neighborhood population densification and changes in cardiometabolic risk among Australian adults*. Oral presentation, **Urban Transitions** conference, November 2018, Barcelona, Spain
4. **Chandrabose M**, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, Giles-Corti B, Sugiyama T. *Urban design and hypertension: systematic review and meta-analysis*. Oral presentation, **Hypertension Beijing** conference, September 2018, Beijing, China

5. **Chandrabose M**, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, Giles-Corti B, Sugiyama T. *Longitudinal relationships of built-environment with cardio-metabolic health: summary of current findings*. Invited speaker, **Designing Healthy Liveable Cities** conference, October 2017, Melbourne, Australia

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1. A Young Investigators Fellowship of the Asian Pacific Society of Hypertension (ASPH) awarded at the 14th congress of ASPH
2. A competitive travel grant of the International Society of Hypertension (ISH) to present the research work at the 27th scientific meeting of ISH

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LIST OF ABBREVIATIONS

AAS – Active Australia Survey

AusDiab – Australian Diabetes, Obesity and Lifestyle Study

BMI – Body Mass Index

CCD – Census Collector Districts

CVD – Cardiovascular Disease

DBP – Diastolic Blood Pressure

FPG – Fasting Plasma Glucose

GIS – Geographic Information System

HDL-C – High-Density Lipoprotein Cholesterol

IRSD – Index of Relative Socioeconomic Disadvantage

MAR – Missing at Random

MAUP – Modifiable areal unit problem

SBP – Systolic Blood Pressure

SLA – Statistical Local Area

TG – Triglycerides

T2D – Type 2 Diabetes

UGCoP – Uncertain geographic context problem

WC – Waist Circumference

2-hr PG – 2-hour Postload Plasma Glucose

ABSTRACT

Neighbourhood built environments may have the potential to impact residents' cardio-metabolic health through physical activity. This Thesis aims to advance the understanding of such potential impacts. This Thesis consists of three published peer-reviewed studies.

Study One, a systematic review and meta-analyses of longitudinal studies, found strong evidence for longitudinal relationships of built environment attributes with cardio-metabolic health among adults. In particular, it found strong evidence for relationships of higher walkability with reduced risks of obesity, type 2 diabetes and hypertension. This systematic review has been published in *Obesity Reviews*.

Two empirical studies were designed to address the gaps identified in the systematic review. These studies were conducted using the Australian Diabetes, Obesity and Lifestyle (AusDiab) study data, which were collected from a national cohort at three time points between 1999 and 2012. The outcomes examined in the empirical studies were 12-year changes in eight cardio-metabolic risk markers: waist circumference; weight; systolic and diastolic blood pressure; fasting and 2-hr postload plasma glucose; high-density lipoprotein cholesterol; and triglycerides. Built environmental attributes for AusDiab study participants were calculated using geographic information systems as an original work of this Thesis. The analytical sample consisted of participants who provided 12-year follow-up data and did not change their residence during the study period.

One gap identified in the systematic review was that most longitudinal studies examined environmental attributes (typically composite measures such as walkability) assessed at one time point, disregarding environmental changes. To address this gap, Study Two examined the relationships of neighbourhood population density increases (densification) on changes in cardio-metabolic risk markers. Densification was calculated using the population density values measured within a 1-km straight-line buffer at three time points in concordance with the AusDiab data collection points. Analysing data from 2,354 eligible participants, higher densification was found related to smaller increases in obesity markers, but it was adversely related to blood pressure and lipid changes. This study has been published in the *Journal of the American Heart Association*.

Study Three investigated the potential mediating role of physical activity (baseline and change) in the relationships between walkability and changes in cardio-metabolic risk markers, as a lack of studies rigorously examining underlying mechanisms of these relationships was another gap identified. For physical activity, self-reported time spent in moderate-to-vigorous physical activity (including walking) was used. A walkability index (consisting of residential density, intersection density, and destinations density) was calculated, within a 1-km street-network buffer using geospatial data sourced around the second follow-up of AusDiab. Analyses of data from 2,023 participants found that higher walkability was related to higher baseline physical activity, which, in turn, was related to smaller increases in obesity markers. There was no evidence for a relationship of higher walkability with a change in physical activity. This study has been published in the *International Journal of Behavioral Nutrition and Physical Activity*.

Collectively, this Thesis adds evidence for potential long-term impacts of the neighbourhood built environment on adult residents' cardio-metabolic health. In particular, higher walkability and higher densification may have protective effects against obesity risk over time. This Thesis also found evidence suggesting that physical activity may partly explain the potential long-term protective effect of higher walkability against obesity risk. However, there were also some unexpected findings, for instance, potential adverse impacts of higher densification on blood pressure and lipid, which warrants further investigation.

The Thesis findings support the potential utility of environmental initiatives to reduce the burden of obesity at the population level through enhancing physical activity. To further advance understanding of the impacts of the built environment on cardio-metabolic health, future research needs to examine diverse built environmental attributes, investigate a broader range of cardio-metabolic health outcomes, and examine multiple pathways between the built environment and cardio-metabolic health.

CHAPTER 1: INTRODUCTION

1.1 Cardio-metabolic Diseases: Burden and Biomedical Risk Factors

Chronic diseases are a major burden to individuals, societies, and governments (1). In particular, cardiovascular disease (CVD) and type 2 diabetes (T2D) are major causes of morbidity and mortality worldwide. It is estimated that 31.0% and 2.8% of all global deaths were caused by cardiovascular disease (number one leading cause) and diabetes (seventh leading cause), respectively, in 2016 (2). In Australia, the prevalence of CVD and T2D among adults were 4.8% and 4.1%, respectively, in 2017–18 (3). The total expenditure on health services in Australia for these 'cardio-metabolic' diseases was $16 billion in 2011–12, which is expected to increase to $58 billion (14% of total health expenditures) in 2031–32 (4). Due to their serious burden, there have been calls for action to tackle the current epidemic of cardio-metabolic diseases, globally and nationally (1, 5).

In the effort to prevent cardio-metabolic diseases, it is important to understand their *biomedical* risk factors and how they may be modified to reduce the likelihood of developing these diseases (6). Biomedical risk factors, which lead to the development of CVD and T2D, include obesity, hypertension, hyperglycaemia, and dyslipidaemia (7). Cardio-metabolic risk markers (i.e., waist circumference, body mass index, blood pressure, blood glucose, and blood cholesterol) and their established diagnostic cut-off values are used to assess individuals' levels of risk (8).

1.2 Strategies to Prevent Cardio-metabolic Diseases

There are two types of strategies for chronic disease prevention: high-risk strategy and population strategy (9). The high-risk strategy focuses on and treats individuals who are diagnosed as being at high risk. Conversely, the population strategy addresses the root causes of diseases for the entire population. To illustrate the difference, Figure 1.1 depicts the distribution of systolic blood pressure of a certain population. The high-risk strategy targets those who are at high risk of developing the disease (e.g., systolic blood pressure over 130 mmHg) and provides treatments to reduce their risk of disease. On the other

hand, the population strategy aims to decrease the blood pressure levels of the whole population by identifying and addressing the population-level causes of the disease.

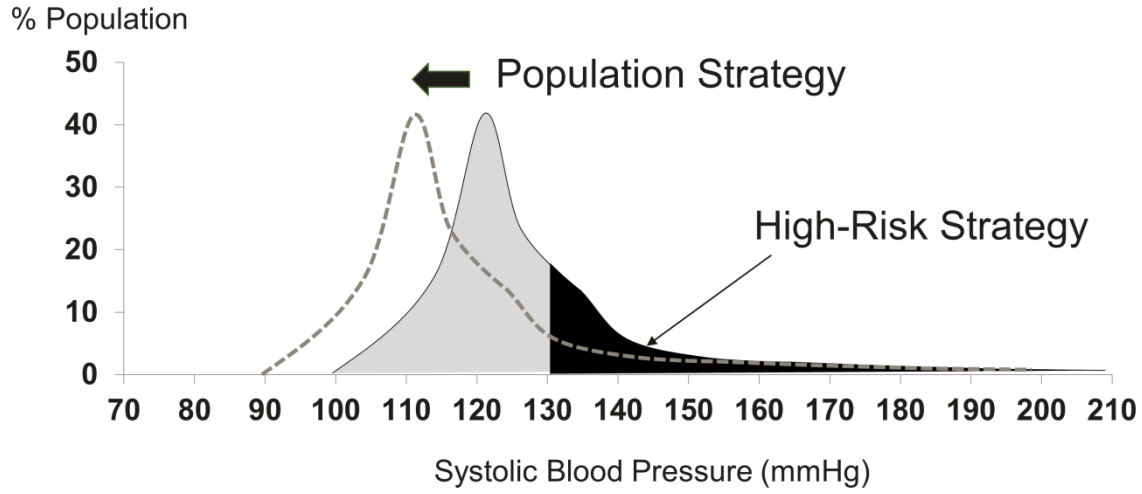

Figure 1.1: High-Risk and Population Strategies for Chronic Disease Prevention

Rose upheld the population strategy in his seminal paper, "Sick individuals and sick populations" (9) as he wrote: "*a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk*". Rose argued that even a small amount of reduction in risk, when achieved for the entire population, can help to substantially reduce the burden of the disease. Adopting the population strategy, this Thesis investigates the potential role of the neighbourhood built environment in reducing the population risk of cardio-metabolic diseases.

1.3 Physical Inactivity: A Behavioural Risk Factor

Population strategies to prevent cardio-metabolic diseases can be implemented by addressing behavioural risk factors. The four common behavioural risk factors relevant to cardio-metabolic diseases are physical inactivity, poor diet, excessive alcohol consumption, and tobacco smoking (10).

Physical activity is defined as any bodily movement produced by the skeletal muscles that require substantial energy expenditure (11). Examples of physical activity include walking, moderate-intensity exercise (e.g., brisk walking, jogging), and vigorous-intensity exercise

(e.g., running) (12). Engaging in regular physical activity is known to provide numerous health benefits (13-15). Physical inactivity, which can be defined as not meeting recommended levels of physical activity for health benefits (e.g., 150 minutes of moderate to vigorous-intensity exercise in a typical week), has been identified as a key behavioural risk factor for cardio-metabolic diseases (16).

Despite the well-known health benefits of physical activity, high proportions of the world's population are physically inactive (17). In Australia, over half of adults (56.4%) did not meet the recommended level of physical activity in 2014–15 (18). Given that physical inactivity is prevalent and a modifiable behavioural risk factor (10), promoting physical activity at the population level is considered an effective strategy for reducing the burden of cardio-metabolic diseases (19).

Conventional approaches to increasing physical activity tended to address an individual's motivation to exercise through various means such as education, incentives, and self-monitoring (20). Physical activity promotion programs focusing on these factors tended to be effective during the program period, but they were less successful in sustaining behavioural changes over time (21). They also work only for a small number of participants who may be interested in being more active. It is now well recognised that strategies focusing only on individual-level factors are unlikely to be sufficient to increase physical activity at the population level (22).

To promote sustained participation in physical activity at a broader scale, it is important to address multi-level factors including individual, social, environmental, and policy factors. This multi-level approach, underpinned by the ecological model of health behaviour (Figure 1.2), has been adopted as a framework to guide interventions to increase physical activity at the population level (23). A key implication of the ecological model is that interventions involving multi-level factors are more effective than conventional individual-level approaches in influencing behaviours (23).

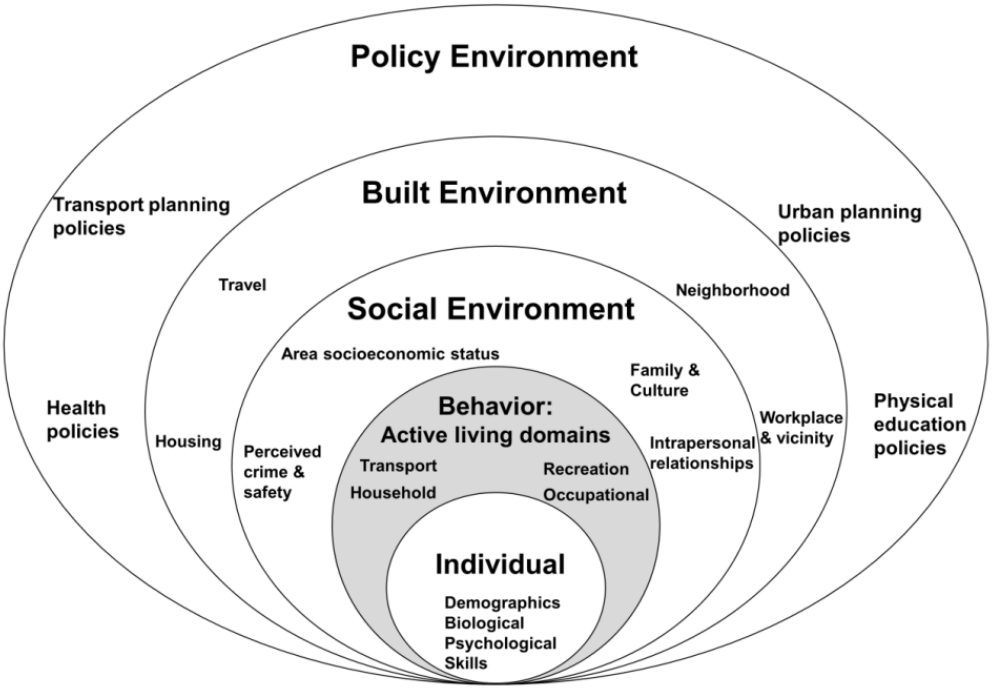

Figure 1.2: The Ecological Model of Physical Activity Behaviour

[adapted from Sallis et al. 2015 (23)]

1.4 Built Environment and Physical Activity

This Thesis seeks to advance understanding of the potential cardio-metabolic health impacts of built environment features through influencing physical activity. The built environment can be defined as "*the part of the physical environment that is constructed by human activity*" (24). The idea of "behaviour settings" is relevant to understand the role of environment in human behaviour: different types of behaviour settings, defined by distinct spatial and physical characteristics, can support or discourage different sets of behaviours (25). Due to the habitual nature of many human behaviours, it is considered that behaviours such as physical activity often occur in response to environmental cues, even in the absence of conscious intentions (26). Thus, features of environmental contexts can act to promote certain behaviours and discourage others. Several domains of the built environment such as housing, neighbourhood, and workplace environments are potentially relevant to physical activity (23). Changing characteristics of these settings has the potential to change people's behaviours. This Thesis focuses specifically on the built environment of neighbourhoods where people live. Recent studies have provided evidence

that improvements in neighbourhood built environments can increase residents' physical activity (27). Physical environmental characteristics, such as air quality, temperature, and noise, are not considered in this Thesis.

The built environment features relevant to physical activity are conceptualised to be fundamentally composed of dimensions known as 3Ds: Density, Diversity, and Design (28). Density can be defined as the number of people or residences per unit area. Diversity refers to the spatial arrangement of different land uses (e.g., residential, commercial, institutional, and recreational). Design refers to the design of streets, which includes their spatial layout (connectivity) and infrastructure for pedestrians. Figure 1.3 depicts two types of neighbourhoods differing in these dimensions: a compact neighbourhood (high in density, diversity, and connectivity) and a sprawling neighbourhood (low in density, diversity, and connectivity). Residents in compact neighbourhoods are postulated to engage in more physical activity than those in sprawling neighbourhoods (28).

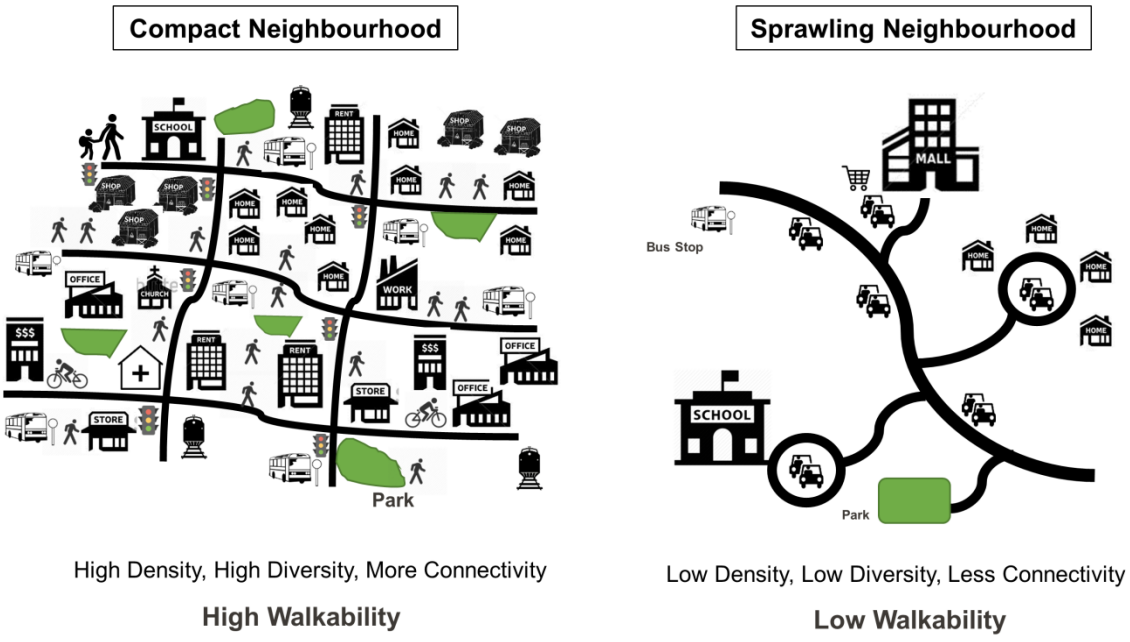

Figure 1.3: Compact Neighbourhood vs Sprawling Neighbourhood

Building on the concept of 3Ds, research has developed a measure of 'walkability' in which several built environmental features are combined to examine relationships between neighbourhood built environments and residents' physical activity levels (29). Numerous

studies have reported associations of higher walkability with higher levels of physical activity (e.g., walking for transport, recreational physical activities) (28-33). Having more destinations in the neighbourhood and pedestrian-friendly routes to such destinations are considered to contribute to residents' active lifestyles (34).

1.5 Built Environment and Cardio-metabolic Health

Given the strong evidence base for the link between neighbourhood built environment and physical activity, environmental initiatives to address physical inactivity are considered as one of the promising strategies to reduce the burden of cardio-metabolic diseases at the population level (35). Over the last two decades, epidemiological studies have been investigating relationships between built environment attributes and cardio-metabolic health outcomes (i.e., risk markers, biomedical risk factors, and incidence of T2D and CVD are collectively referred to as cardio-metabolic health outcomes in this Thesis) (36). Existing studies on this topic have produced mixed yet promising findings (37). This Thesis seeks to enhance understanding of this topic, building on these existing studies. A systematic review summarising the current state of knowledge is discussed in Chapter 2.

1.6 Conceptual Framework of the Thesis

Recently, Giles-Corti and colleagues presented a comprehensive framework for the relationships between the built environment and cardio-metabolic health (38). The framework presented is complex and involves multiple pathways that include behaviours (e.g., physical activity, diet) and risk exposures (e.g., air pollution, noise pollution). Within this framework, this Thesis focuses on the relationships between the built environment and cardio-metabolic health outcomes that are postulated to be linked through physical activity, as illustrated in Figure 1.4.

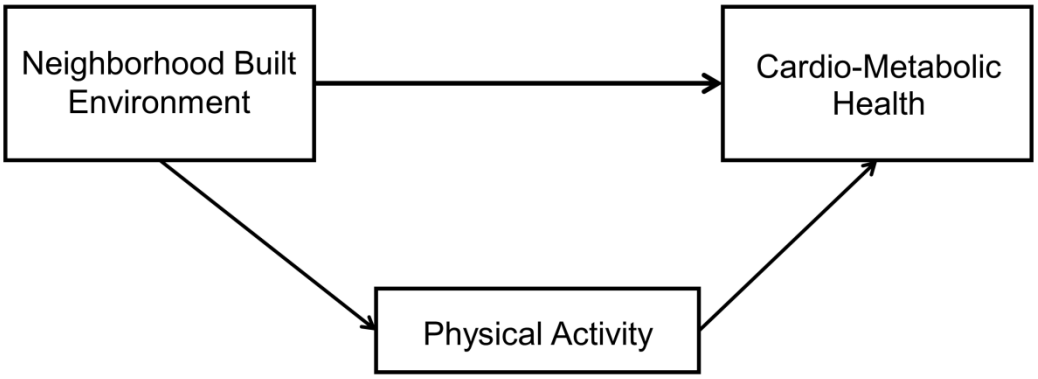

Figure 1.4: The Conceptual Framework of the Thesis

1.7 Research Aims of the Thesis

The broad aim of this Thesis is to advance the understanding of the potential impacts of the neighbourhood built environment on adult residents' cardio-metabolic health. More specifically this Thesis aimed:

1. To review existing studies to understand the current status of knowledge on the potential impacts of the built environment on cardio-metabolic health;
2. To further investigate the relationships between the built environment and cardio-metabolic health based on the gaps identified in the review; and
3. To examine the potential mediating role of physical activity in the relationships between the built environment and cardio-metabolic health.

A systematic review and two empirical studies were conducted to address these aims. Gaps identified in the systematic review informed the development of research questions for the empirical studies.

Ultimately, findings of this Thesis are expected to provide insights into built environmental features that may be protective against cardio-metabolic diseases, which are of relevance to researchers, policy-makers, and practitioners involved in public health and urban planning. The findings may contribute to developing future environmental initiatives to reduce the burden of cardio-metabolic diseases at the population level by addressing physical inactivity.

1.8 Structure of the Thesis

This Thesis comprises six chapters. Following the introduction (Chapter 1), Chapter 2 presents the literature review and discusses specific research questions investigated in the empirical studies. Chapter 3 describes the methodology for two empirical studies undertaken in this Thesis. Chapters 4 and 5 present two empirical studies, in which specific research questions were investigated. The final chapter, Chapter 6, discusses a summary of the findings, their implications, and future research directions.

CHAPTER 2: LITERATURE REVIEW

This Chapter is divided into four sections. First, a brief review of research on the built environment and cardio-metabolic health among adults is presented. This is followed by a published article of the systematic review that was conducted as a part of this Thesis. Building on the gaps identified in the systematic review, this Chapter discusses specific research questions investigated in the empirical studies.

2.1 A Review of Research on Built Environment and Cardio-metabolic Health

2.1.1 Background

The following three studies, published in 2003, can be considered as the pioneer empirical studies in this field (39). Giles-Corti and colleagues examined the associations between a number of built environment attributes and obesity status among 1,755 residents in Perth, Australia (40). They reported that residents with poor access to recreational facilities, perceiving no retail stores, and perceiving no walking or cycling paths in the neighbourhood were more likely to be obese. Saelens and colleagues developed a neighbourhood walkability index using residential density, land use mix and street connectivity and found that residents of low-walkability neighbourhoods had higher body mass index (BMI) than those of high-walkability neighbourhoods, in a sample of 107 adults who resided in San Diego, the USA (41). Analysing data from a sample of 206,992 adults residing across 448 counties in the USA, Ewing and colleagues reported that higher levels of sprawl (lower population density and street connectivity) were associated with higher BMI and a greater prevalence of hypertension but not with the prevalence of T2D (42).

After these early studies, empirical research investigating relationships between the built environment and cardio-metabolic health has grown gradually over the last 15 years (36, 37). However, studies conducted to date are mostly cross-sectional in design, which does not allow causal inferences to be made for these relationships (36, 37).

2.1.2 Study designs in built environment and health research

Experimental study design involving randomisation is needed to establish causal relationships (43). However, such a design is highly impractical in research on neighbourhood and health, because it requires randomly assigning different neighbourhoods to study participants (43). Most studies in this research field generally employ observational study designs. Observational study design can include both cross-sectional and longitudinal studies. Although cross-sectional studies are useful as they can provide preliminary evidence to the scientific and policy-making communities (44), their key limitation is the inability to establish "*temporal ordering*" of exposures and outcomes, which is one of the requirements to support causality (44). For example, people with better cardio-metabolic health profiles may have chosen to live in neighbourhoods that are supportive of physical activity, rather than such neighbourhoods affecting their health (45). Cross-sectional studies cannot rule out such reverse causation. Longitudinal design, on the other hand, allows investigation of relationships of exposures with subsequent changes in outcomes (46). Although participants are not randomised, the longitudinal study design is a step closer to identifying causal relationships between the built environment and cardio-metabolic health (43).

2.1.3 Review of systematic reviews

To determine the prevalence of longitudinal studies in the literature of the built environment and cardio-metabolic health among adults, the candidate conducted a review of systematic reviews. Two electronic databases (Medline and Web of Science) were searched using a combination of three sets of keywords related to "built environment", "cardio-metabolic health", and "review", for systematic reviews published in peer-reviewed journals up to January 2016. This search was supplemented by a review of systematic reviews on the built environment, physical activity, and obesity, published in 2012 (47). Six relevant systematic reviews were identified (36, 37, 39, 48-50). Table 2.1 summarises the characteristics of those systematic reviews identified.

Table 2.1: Characteristics of Systematic Reviews on Built Environment and Cardio-Metabolic Health among Adults

Lead Author (Year Published)	**Cardio-metabolic health outcomes**	**Number of Studies identified†**	**Number of longitudinal studies**
Booth (2005)	Obesity-related	4	0
Papas (2007)	Obesity-related	10	0
Black (2008)	Obesity-related	10	0
Feng (2010)	Obesity-related	35	0
Leal (2011)	Multiple outcomes	40	4
Mackenbach (2014)	Obesity-related	70	5

Note: † In each review, different types of studies were reviewed according to the scope of the review. Only those studies examining relationships of built environment attributes and cardio-metabolic health outcomes among adults are reported here (studies investigating other environmental factors such as food environments and those targeting children/adolescents are not included).

As shown in Table 2.1, studies identified by the existing systematic reviews were predominantly cross-sectional in design. No longitudinal study was included in the earlier reviews published before 2010 (39, 48-50). The two reviews published after 2011 had a small number of longitudinal studies (36, 37). In addition, all reviews focused on obesity as the health outcome, except one review (36) that included a few studies (mostly cross-sectional) examining relationships of built environment attributes with measures related to hypertension (n=5), hyperglycaemia (n=4), and dyslipidaemia (n=1).

Given an expected increase in the number of longitudinal studies since 2013 when the latest review searched the literature (37), a new systematic review of longitudinal studies was warranted to understand the current knowledge on the potential impacts of the built environment on cardio-metabolic health.

2.2 Built Environment and Cardio-metabolic Health: Systematic Review and Meta-Analysis of Longitudinal Studies (published peer-reviewed paper)

This systematic review was conducted as the first study of this Thesis (referred to as **Study One**) by the candidate with contributions of the supervisors and three other co-authors.

The nature and extent of contributions of authors are shown in Appendix I. This manuscript has been published in *Obesity Reviews*.

Citation:

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Obesity Comorbidity/Etiology

Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies

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Summary

Built environment attributes may be related to cardio-metabolic diseases (e.g. type 2 diabetes, heart disease and stroke) and their risk factors, potentially by influencing residents' physical activity. However, existing literature reviews on the built environment and health for the most part focus on obesity as the outcome and rely on cross-sectional studies. This systematic review synthesized current evidence on longitudinal relationships between built environment attributes and cardio-metabolic health outcomes among adults and on the potential mediating role of physical inactivity. By searching eight databases for peer-reviewed journal articles published in the English language between January 2000 and July 2016, the review identified 36 articles. A meta-analysis method, *weighted Z-test*, was used to quantify the strength of evidence by incorporating the methodological quality of the studies. We found strong evidence for longitudinal relationships of walkability with obesity, type 2 diabetes and hypertension outcomes in the expected direction. There was strong evidence for the impact of urban sprawl on obesity outcomes. The evidence on potential mediation by physical activity was inconclusive. Further longitudinal studies are warranted to examine which specific built environment attributes influence residents' cardio-metabolic health outcomes and how physical inactivity may be involved in these relationships.

Keywords: Hypertension, obesity, type 2 diabetes, walkability.

Introduction

Type 2 diabetes (T2D) and cardiovascular disease (CVD) are leading causes of poor health, disability and death, and their burden is rising globally (1,2). There are established markers of cardio-metabolic risk, including abdominal adiposity, glucose intolerance, hypertension and dyslipidaemia, which can predispose individuals to developing T2D and CVD (3). Given that T2D and CVD are regarded as having significant preventable components (4,5), there have been calls for population-wide public health initiatives to address their major behavioural risk factors, which include physical inactivity, unhealthy diet and cigarette smoking (6). Considering that physical inactivity is highly prevalent worldwide (7), there is growing interest in the role of neighbourhood built environments, which potentially support residents' active lifestyles, in preventing cardio-metabolic diseases (8,9).

A number of systematic reviews of studies on relationships between built environment attributes and adults' cardio-metabolic health outcomes have been published (10–17). However, these reviews summarized evidence based mostly on cross-sectional studies; hence, they do not support causal inferences. In addition, these systematic reviews focused primarily on obesity-related outcomes, with only a few considering a range of cardio-metabolic health outcomes (14,16). Evidence from longitudinal studies needs to be synthesized to identify attributes of built environments that may be protective against the development of T2D and CVD (9).

Built environment attributes may influence residents' health, partly through physical activity and sedentary behaviour (18). The ecological model of health behaviour postulates that multilevel factors (e.g. individual, social, environmental and policy) can influence behaviours, emphasizing the role of 'behaviour settings' – those attributes of environmental contexts that can act to promote certain behaviours and discourage others (19). Identifying the built environment attributes that are supportive of habitually active lifestyles is a public health research priority. Environmentally focused initiatives are argued to have the potential to be effective, even in the absence of a conscious intention, e.g. to be physically active (20). Previous studies show that lack of physical activity and prolonged sedentary behaviour can independently elevate the risk of developing T2D and CVD (21,22). Literature reviews also identify consistent relationships between certain built environment attributes (e.g. residential density, street connectivity, availability of diverse destinations, public open space (POS) and their composite measures such as walkability) and different types of physical activities (e.g. walking and leisure-time physical activity) and sedentary behaviours (e.g. car use and television watching) in adults (23–26). However, it is not clear to what extent these behaviours may mediate longitudinal relationships between built environments and cardio-metabolic health.

We systematically reviewed longitudinal studies on the relationships between built environment attributes and cardio-metabolic health outcomes in adults and quantified the strength of evidence using a meta-analytic approach that accounted for the methodological quality of the studies. We also synthesized any relevant evidence on how physical activity and sedentary behaviour may mediate the longitudinal relationships.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (27) were followed in this review.

Search strategy

A reproducible systematic search of peer-reviewed journal articles published in the English language between January 2000 and July 2016 was undertaken by the first author (M. C.) using eight electronic databases: Medline, Web of Science, Cochrane, Embase, PsycInfo, CINAHL, Scopus and Transport Research International Documentation. Three sets of search terms on built environment, cardio-metabolic health and longitudinal design were used. Search terms for each category were developed based on those used in other related reviews (14,15,26,28). A full description of the search terms is provided in Table S1.

Inclusion/exclusion criteria

Studies were included if they met the following four criteria:

1. *Exposures*: Objectively measured (using geographic information systems) or perceived (using questionnaires) built environment attributes;
2. *Outcomes*: Objectively measured (by biomedical examination) or self-reported (using questionnaires) cardio-metabolic health outcomes, including incidence of diseases and biomarkers;
3. *Study designs*: Longitudinal design quantitatively examining the relationships between exposures and outcomes; and
4. *Participants*: Adults, aged 18 years and older.

One exclusion criterion was based on how studies postulated a link between the built environment and cardio-metabolic health. To sustain a manageable scope and coherence, we focused on studies that postulated physical activity or sedentary behaviour as a pathway and excluded studies postulating other mechanisms, such as food environment, air/noise pollution, access to health care, sanitation and climate change. We also excluded studies focused specifically on clinically defined subgroups (e.g. those who were

pregnant, with diabetes and had stroke) and those studies focusing on participants' workplace and its vicinity.

Screening process

Articles were reviewed independently by three authors (M. C., J. R. and L. G.). At all stages of the review process (title and abstract screening, full article selection and data extraction), M. C. reviewed 100% of the articles, with J. R. and L. G. each reviewing 60% of the articles with an overlap of 20%. Discrepancies between the reviewers at each stage were mediated by T. S.

Data extraction

The following information was extracted from each article:

1 *Study*: author, year (published), project/cohort name;
2 *Location*: country, multisite or not;
3 *Sample*: size, demographic information, recruitment strategy (particularly, if study areas were purposefully selected to have a diversity in environmental attributes or not);
4 *Design*: study design (observational, natural experimental), follow-up duration, number of waves, residential relocation;
5 *Response rate*: at baseline, retention at follow-up(s);
6 *Measures*: outcomes (including methods), exposures (including methods, area unit and examined environmental changes or not), mediators, moderators, individual-level and area-level confounders;
7 *Analyses*: statistical methods, accounting for area-level clustering or not, adjusting for residential self-selection or not and drop-out analysis; and
8 *Results*: magnitude and direction of relationships, statistical significance, mediation (physical activity and/or sedentary behaviour)

Coding and counting of findings

A statistically significant relationship was coded as [E] if it was in the expected direction (i.e. built environment attributes supporting physical activity, such as high walkability, being associated with reduced cardio-metabolic risk) or [U] if it was in the unexpected direction. A statistically non-significant relationship was coded as null [N]. To avoid over-representation of findings from the same data set, reported relationships in the articles were counted using a method introduced in a previous review (23): if the relationship of a specific environmental exposure with a specific cardio-metabolic outcome (e.g. walkability and obesity) using the same data source was reported in more than one article, the finding from the article that scored a higher methodological quality score (detail explained in the next section) was counted; if an article examined a specific exposure–outcome relationship within a study using the exposure calculated in different types of geographical units (e.g. administrative units and individual buffers) or at different scales (e.g. 400- and 1,000-m buffers), each finding was assigned an equal fractional weight in such a way that the sum of the weights equals to one; and if a specific exposure–outcome relationship was examined separately for subgroups (e.g. men and women) within a study, the findings were considered as distinct only if they differed in direction or statistical significance. In such cases, each finding was assigned a fractional weight proportional to the sample size of the subgroup.

Methodological quality assessment

It is recommended that systematic reviews of built environment and health research should consider the methodological quality of the reviewed articles to synthesize and interpret the findings (29). Cerin *et al.* developed a quality assessment tool to assess the methodological quality of cross-sectional studies on built environment attributes and physical activity (23). Barnett *et al.* (30) extended this tool by adding an item to assess the study design. The assessment items in the original tool included [1] sample representativeness; [2] study design; [3] exposure variability (study areas selected to maximize the variability in the exposure variables); [4] adjustment for individual socio-demographic covariates; [5] adjustment for residential self-selection; [6] accounting for area-level clustering; and [7] appropriate presentation of analysis results. We adapted and further extended this tool by adding items relevant to longitudinal design, measurement of built environment attributes, and measurement of cardio-metabolic health outcomes. For aspects relevant to longitudinal design, we included the following items based on the quality assessment checklist developed by Tooth *et al.* (31): [8] follow-up duration; [9] number of data collection time points; [10] participant retention rate; and [11] appropriate longitudinal data analysis. We further included items specific to the measurement of exposures and outcomes, following Giles-Corti *et al.* (32). These included [12] measurement of built environment attributes (appropriate geographical unit and size to capture participants' neighbourhood for objective measures or use of validated survey instruments for perceived measures); [13] measurement of health outcome (objectively measured vs. self-reported); and [14] temporal match of exposure and outcome measures.

For each assessment item, a score of 0.0 (not meeting the quality criterion) or 1.0 (meeting the quality criterion) was assigned. An intermediate score of 0.5 was assigned for an acceptable level for relevant items. Items 6, 7 and 11 (used for assessing the quality of statistical analysis) were assigned a score of 0 or 1/3 to avoid over-scoring for statistical

methods (23). We also assigned an additional score to each study according to its sample size as described in Cerin *et al.* (23). Each study was assigned the total assessment score (the sum of methodological quality and sample size scores), which was then used to assess the strength of evidence (detail explained in the next section). The quality assessment tool with rationale for scores assigned to each item is described in Table S2.

Assessing the strength of evidence

Conducting a traditional meta-analysis using models that include effect sizes of reported associations is difficult due to heterogeneities in environmental exposure measures between studies. An alternative meta-analysis method, known as *weighted Z-test* (33), was used to combine findings of multiple independent studies and to assess the strength of the evidence. This approach has been used in recent reviews of the built environment and physical activity literature (23,30). A conservative z-value was assigned to each reported relationship according to the level of significance (α) stated in the study (for statistically significant finding in the expected direction: $z = 1.96$ for $\alpha = 0.05$ and $z = 1.64$ for $\alpha = 0.10$; $z = 0.00$ for null; for statistically significant findings in the unexpected direction: $z = -1.96$ for $\alpha = 0.05$ and $z = -1.64$ for $\alpha = 0.10$). Each reported finding was separately assessed according to the counting method described earlier. For a specific exposure–outcome relationship, a *weighted Z* value was calculated by summing z scores using the total assessment scores of the studies as *weights* and dividing it by the square root of the sum of squared *weights*. The two-tailed p-value associated with the *weighted Z* value was then calculated and used to determine the strength of the evidence using the following criteria: $p < 0.05$-weak evidence; $p < 0.01$-strong evidence; and $p < 0.001$-very strong evidence (34). This meta-analytic approach was conducted only if a specific exposure–outcome relationship was reported five or more distinct times among the reviewed articles to meet the methodological standards for meta-analysis (35). If a specific relationship was reported four or less distinct times, it was considered insufficient to determine the strength of evidence. This meta-analytic approach, which accounts for the methodological quality of the study, quantifies the strength of evidence more accurately (in comparison with the approach of counting the number of significant associations) and provides a better assessment of the current evidence base (23).

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining the process of literature searching and article screening is provided in Fig. 1. The initial systematic search across the eight databases produced 6,749 [3,402 unique] articles. After a sequence of independent assessment steps, 36 articles (36–71) were included in the review.

Characteristics of reviewed studies

The data extracted from all the articles included in the meta-analysis are presented in Table S3. Key characteristics of the articles are summarized in Table 1.

General study characteristics

More than one half of the articles were based on studies conducted in the United States (56%), followed by Canada (14%), Sweden (11%) and Australia (8%). Over 70% of the articles were published after 2013. With regard to geographical settings, most studies (78%) were conducted in urban areas only. The majority of studies recruited

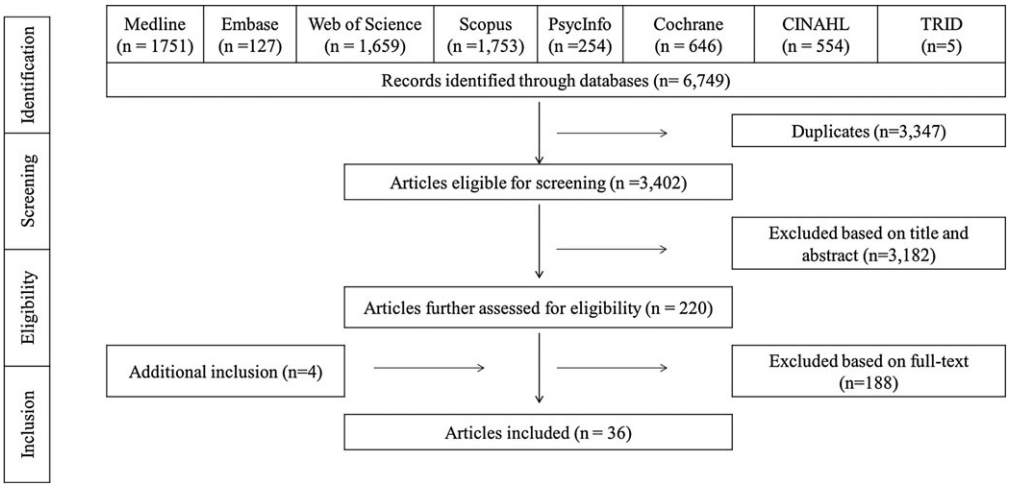

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. TRID, Transport Research International Documentation.

Table 1 Key characteristics of the 36 articles reviewed

Item	Category (number of articles)
Country	United States (20); Canada (5); Sweden (4); Australia (3); Finland (1); Germany (1); Lithuania (1); Wales (1)
Publication year	2007 (1); 2009 (4); 2010 (2); 2011 (2); 2013 (7); 2014 (8); 2015 (4); 2016 (7); 2017 (1)
Geographical setting	Single-site [urban] (14); multisite [urban] (14); multisite [urban + rural] (7); not reported (1)
Gender	Both (29); women only (5); men only (2)
Age group	Middle-to-older aged adults (16); all adults (8); older adults (4); younger-to-middle aged adults (3); middle aged adults (3); younger adults (2)
Baseline sample size	200–500 (3); 501–1,000 (4); 1,001–6,000 (20); 15,000–50,000 (4); 500,000–5,000,000 (5)
Study design	Observational (35); natural-experimental (1)
Mean follow-up duration	Less than 2 years (3); 2–5 years (8); 5+ years (25)
Number of waves	2 waves (14); 3 waves (3); 4 waves (3); 5 waves (5); 6 waves (1); 7 waves (2); regional administrative health registries (6); not reported (2)
Relocation status	Stayers only (17) [reported (6); assumed (11)]; movers only (7); both (12)
Cardio-metabolic health outcomes	Obesity related [body mass index (14); waist circumference (6); obesity incidence (4); body weight (2)]; type 2 diabetes related [type 2 diabetes incidence (6); fasting glucose (1); HOMA-IR (1); HbA_{1c} (1)]; hypertension related [hypertension incidence (4); systolic/diastolic blood pressure (3)]; cardiovascular disease events (5); others [triglycerides (2); LDL cholesterol (2); HDL cholesterol (2); dyslipidaemia (2); metabolic syndrome (1); C-reactive protein (1)]
Built environment exposure variables	Walkability (20); recreational facilities (13) [public open space (5)]; urban sprawl (5); destinations [public transport stops (2); retail and community destinations (1)]; routes [street connectivity (3); traffic intensity (3); safety (2); amount of slope (1)]; other composite measures (5); residential density (2); land-use mix (2)
Built environment measurement methods	GIS measures (33) [scales: administrative unit (14); straight-line buffer (11); street-network buffer (8); distance measure (7)]; perceived measures (7) [scales: within 15- to 20-min walk from home (6); residential address (1)]
Longitudinal measures	Outcome [changes in health outcomes (20); incidences of health outcomes (19)]; exposure [single time point environment measures (29); multiple time points environment measures (7)]; temporal match of single time point exposure and outcome [matched (23); mismatched (3); not reported (3)]

GIS, geographic information system; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HbA_{1c}, Haemoglobin A1c.

participants from multiple sites (38% from urban areas, 19% from both urban and rural areas). The sample sizes of the articles reviewed ranged from 262 to over 4 million. While the majority of articles used data collected in cohort studies (84%), six articles used data from national or state health registries, which were not primarily established for particular research purposes. The large-sample studies used such health registry data.

Research design aspects

Almost all the articles reviewed were based on observational studies. One natural-experimental study (37), which met our inclusion criteria (a longitudinal study on built environment and cardio-metabolic health), examined body mass index (BMI) changes among those who were assigned different residential locations (with little to no control over their neighbourhood placement) after Hurricane Katrina. The follow-up duration ranged from less than 1 to 18 years. In cohort studies, data were collected at two waves in about two-fifths of the studies, while two studies collected data across seven waves. However, it should be noted that environmental attributes were measured only once in most studies (over 80%). Of these, a majority (n = 23) used single time point exposure measures that temporally matched with the study period (often at baseline), three used exposure data measured outside the study period and three did not report the time point in which exposure data were collected. Seven studies used built environment attributes measured at multiple time points concurrent with health data collection. About half of the articles (n = 17) examined participants who did not relocate to a new address (stayers) during the study period. However, 11 of these appear to have assumed that participants did not relocate during follow-ups without checking their relocation status. About 10% of the articles focused only on those who relocated (movers), and one third of the articles included both stayers and movers in their sample.

Outcomes

Obesity outcomes (incidence of obesity, BMI, waist circumference and body weight) were examined in 60% of the articles reviewed. Of the 17 articles using BMI measurements, nine used objectively measured height and weight, and eight used self-reported measures. T2D outcomes (incidence of T2D, fasting glucose, HbA1c and HOMA-IR) were examined in a quarter of the articles. Hypertension outcomes (incidence of hypertension and systolic/diastolic blood pressure) were examined in 20% of the articles. CVD events (incidence of coronary heart disease or stroke or mortality due to CVD) were examined in 14% of the articles. All articles that examined outcomes related to T2D, hypertension and CVD used objectively collected data (i.e. measured by biomedical examination or retrieved from registry records), except two studies (49,52) in which self-reported outcomes were used. Outcome variables were characterized as either changes in continuous measures (e.g. BMI change from

baseline to follow-up) or incidences of adverse events (e.g. development of T2D at follow-up).

Exposures

A variety of built environment attributes were examined in the articles reviewed. Neighbourhood walkability, a composite measure of environmental supportiveness for walking, consisting typically of objectively measured residential density, street connectivity and land use diversity (n = 16) or using similar self-reported items measuring perceived environments (n = 4), was the most frequently used exposure variable. Another frequently examined exposure was the presence/proximity of neighbourhood recreational facilities such as gyms and parks (n = 13). Urban sprawl index, which is another composite measure, calculated similar to walkability but involving a degree of centring (concentration of population/employment within an area), was used in five studies. To synthesize findings in a succinct manner, other non-composite built environment attributes were classified into two categories: destinations and routes (25). In the current review, the destination category included presence/proximity of public transport stops and other local (community and retail) destinations. The route category included street connectivity, traffic intensity, perceived safety and the amount of slope. Two articles (42,54) included composite measures, which were constructed in ways that are different from walkability and urban sprawl indices. For example, *neighbourhood development intensity* consisted of population density, road density and resource (food, physical activity and inactivity resources such as movie theatres) density (42).

The majority of articles used geographic information systems to measure built environment attributes (n = 33), while seven articles used perceived environmental characteristics (four studies used both). No audit measures were used in the articles identified. Of the studies using geographic information systems measures, administrative units were the most frequently used area unit (n = 15), followed by straight-line (circular) buffer areas around participant's residence (n = 11), street-network buffer areas that can be reached within a certain distance from residence using street network (n = 7) and distance measures (proximity of destinations from residence, n = 7). Straight-line and street-network buffer sizes ranged from 400 m to 3 km. Five out of seven articles that used perceived environmental measures were from the Multi-Ethnic Study of Atherosclerosis study. The Multi-Ethnic Study of Atherosclerosis study asked participants to rate the suitability of the environment for physical activity (multiple items) within 1 mile or a 20-min walk from home.

Analytical approaches

The statistical methods used varied widely according to data type, study characteristics and research questions. For instance, statistical approaches included modelling continuous outcome variables (linear regression models); modelling binary outcome variables (logistic regression models); modelling incidences of outcome events at follow-up (proportional hazard models); modelling within-person changes in exposures and outcomes by controlling for time-invariant confounders (fixed-effects models); and modelling concurrent trajectories of exposures and outcomes (latent growth models). Analysis accounted for area-level clustering through the use of multilevel regression models or robust (sandwich-type) standard errors. Studies adjusted for potential confounding factors including individual-level sociodemographic covariates (n = 33); behavioural covariates (n = 23); comorbid conditions (n = 20); area-level socioeconomic variables (n = 23); and residential self-selection (directly by adjusting for preference or attitudinal measures [n = 2] or by alternative approaches [n = 9] such as use of fixed-effects models or propensity-score matching technique). Two-thirds of the studies examined effect modifications (n = 24). Further details of analytical approaches used in the articles are provided in Table S3.

Methodological quality assessment

Table 2 shows the summary of quality assessment. The full quality assessment results are provided in Table S4. The highest possible quality score is 12.0. The mean (SD) quality score was 7.5 (1.1).

Summary of findings

Table 3 presents the summary of findings for longitudinal relationships between built environment attributes and cardio-metabolic health outcomes. The table summarizes findings for each of which the relationship was reported five or more distinct times. The *Aggregated* columns list the number of significant findings (in the expected direction) of the total number reported, with corresponding percentage and number of articles that examined those relationships. The *Meta-analysis* columns list the *weighted Z-value* with the associated p-value calculated in the meta-analysis. The complete meta-analysis results are provided in Table S5. In the following, we use the term 'case' rather than 'study' to describe a specific finding, as one study can examine many relevant relationships.

Walkability

Meta-analysis found strong evidence for longitudinal relationships of neighbourhood walkability with obesity and T2D outcomes. Very strong evidence was found for the impact of walkability on hypertension. Other cardio-metabolic health outcomes (CVD, triglycerides, cholesterol, metabolic syndrome, C-reactive protein and dyslipidaemia) were examined in a limited number of studies (<3 cases, not reported in Table 3). Studies employed different

Table 2 Summary of quality assessment for the 36 articles

	Quality assessment item	# of studies meeting the criterion (%)	Average score
1	Sample representativeness [response rate ≥ 60% or sample shown to be representative of the population]	27 (75%)	0.75
2	Study design [natural experiment]†	1 (3%)	0.51
3	Exposure variability [recruitment stratified by key built environmental attributes]	3 (8%)	0.08
4	Individual confounding [adjustment for at least age, gender, education or similar]	33 (92%)	0.92
5	Residential self-selection [directly adjusted]†	3 (8%)	0.21
6	Area-level clustering [accounting for area-level clustering in analysis for multilevel sampling]	25 (69%)	0.23
7	Appropriate presentation of analysis results	29 (81%)	0.27
8	Follow-up duration [5+ years]†	25 (69%)	0.81
9	Number of data collection time points [3+ waves]†	13 (36%)	0.68
10	Participant retention [retention rate ≥ 80% or drop-outs are comparable with follow-up participants]†	18 (50%)	0.68
11	Appropriate longitudinal data analysis	36 (100%)	0.33
12	Built environment measurement [street-network buffer for objective measures or use of validated survey instruments for perceived measures]†	9 (25%)	0.64
13	Health outcome measurement [objective measurement]†	26 (72%)	0.86
14	Temporal match of exposure-outcome measures [multiple time points exposure measures concurrent with outcome measures]†	7 (19%)	0.51

†Intermediate score (0.5) was also given.

Table 3 Summary of findings for longitudinal relationships between built environment attributes and cardio-metabolic health outcomes

Built environment attributes	Cardio-metabolic health outcomes					
	Obesity		T2D		Hypertension	
	Aggregated	Meta-analysis	Aggregated	Meta-analysis	Aggregated	Meta-analysis
Walkability	9/20 (45%) [13]	2.925 p = **0.003**	4/7 (57%) [7]	2.944 p = **0.003**	4/6 (67%) [6]	3.349 $p <$ **0.001**
- Walkability (objective measures only)	7/17 (41%) [11]	2.379 p = **0.017**	3/6 (50%) [6]	2.357 p = **0.018**	3/5 (60%) [5]	2.793 p = **0.005**
Recreational facilities	6/11 (55%) [7]	2.408 p = **0.016**	– [2]	–	– [2]	–
- Green space/parks	2/5 (40%) [4]	1.034 p = 0.301	– [1]	–	– [1]	–
Urban sprawl	3/6 (50%) [4]	2.989 p = **0.003**	–	–	–	–
Destinations [public transport, retail, community]	2/6 (33%) [2]	1.499 p = 0.134	–	–	–	–
Route attributes [street connectivity, traffic, safety, slope]	3/8 (38%) [3]	1.687 p = 0.092	– [2]	–	– [2]	–
Other composite measures	2/5 (40%) [2]	1.764 p = 0.077	– [2]	–	– [1]	–
Total	25/56 (45%) [21]	–	9/14 (63%) [9]	–	5/11 (45%) [7]	–

Aggregated columns show the number of significant (E) findings among the total cases reported, along with corresponding percentage, [number of independent articles] examined the specific relationship. *Meta-analysis* columns show the *weighted Z-value*, along with associated *p*-value calculated in the meta-analysis. Statistically significant evidence is shown in bold. A positive *weighted Z-value* indicates that the relationship is in the expected direction. Percentage and meta-analysis results are reported only if relationship was examined five or more distinct times among the reviewed articles. T2D, type 2 diabetes.

methods in constructing objectives measures of walkability (i.e. built environment attributes included, buffer type and size, and composition method) (Table S3). The strength of the evidence for longitudinal relationships of objective walkability measures (i.e. excluding perceived measures) with obesity, T2D and hypertension outcomes was attenuated but remained significant. Perceived walkability was found to be consistently related with different health outcomes, including obesity outcomes (36,39), T2D incidence (47) and hypertension incidence (55). However, there were

insufficient cases to assess the strength of the evidence for perceived walkability measures alone.

Recreational facilities

Weak evidence was found for longitudinal relationships between neighbourhood recreational facilities and obesity outcomes. Because most of the studies that examined recreational facilities as exposures did not provide explicit information on whether parks and other POSs were included or not, we combined them with the studies that focused on access to green spaces or parks. Meta-analysis found no evidence for longitudinal relationships between access to green spaces or parks and obesity outcomes. There were insufficient cases that examined relationships of neighbourhood recreational facilities with T2D, hypertension or CVD outcomes.

Urban sprawl

Meta-analysis found strong evidence for the impact of urban sprawl on obesity outcomes. Urban sprawl and walkability were both composite measures often constructed using similar components. A major difference between them is that walkability was measured within a smaller local area (e.g. census block in the USA, a buffer area around home), while urban sprawl was measured at a much larger scale such as counties or metropolitan statistical areas in the USA (37,49,58,64) and included a degree of centring (72). No studies examined longitudinal relationships of urban sprawl with T2D or hypertension outcomes.

Destinations, routes and other composite measures

No evidence was found for longitudinal relationships of destinations (public transport stops, retail and community places), route attributes (street layout, amount of slope and traffic intensity) and other composite measures with obesity outcomes. There were insufficient cases that examined longitudinal relationships of these environmental measures with T2D, hypertension or CVD outcomes.

Mediation by physical activity and sedentary behaviour

One fourth of the articles attempted to examine whether longitudinal relationships between built environment attributes and cardio-metabolic health outcomes were mediated by participants' physical activity (Table S3). However, almost of all of these studies tested the mediation effect simply by checking whether adjustment for physical activity (mostly with other potential mediators such as diet) attenuated the associations. This analytical approach is often ineffective to accurately estimate mediating effects (73). Thus, in the current review, the evidence for the mediating role of physical activity in the relationships examined is inconclusive, due to the limitation in analytical approaches. Nevertheless, one Australian study (71) tested the indirect effect of walkability on 10-year change in HbA_{1c} through self-reported physical activity using structural equation modelling and found a partial mediation effect. None of the articles reviewed examined mediation by sedentary behaviour.

Results stratified by relocation status

The studies reviewed can be categorized according to relocation status: stayers (reported), stayers (assumed) and movers. Table 4 shows the percentage of significant findings for each relocation status. It was found that studies on stayers (particularly, on those who were confirmed to stay in the same location) had a higher percentage of significant findings, compared with the studies on movers.

Discussion

Impact of built environment attributes on cardio-metabolic health

To our knowledge, this is the first systematic review of longitudinal studies that examined relationships between built environment attributes and cardio-metabolic health outcomes. Studies using longitudinal designs are recommended to better understand the potential causal effects of built environments on health outcomes (15,17). Based on meta-analysis of existing longitudinal studies, this review found evidence suggesting causal relationships between living in a particular environment and change in cardio-metabolic health.

We found very strong evidence for the longitudinal relationships of walkability with hypertension outcomes. Strong evidence was found for the impact of walkability on obesity and T2D outcomes and for the impact of urban sprawl on obesity outcomes. A recent systematic review by Mackenbach *et al.* (15) reported inconsistent findings for the relationships between walkability and obesity outcomes but consistent relationships between urban sprawl and obesity in North America. Another systematic review by Grasser *et al.* (13) also reported inconsistent findings for the relationships between walkability and obesity outcomes.

Table 4 Aggregated results for studies on stayers and movers

	Stayers (reported)	Stayers (assumed)	Movers
Total	11/19 (58%)	11/22 (50%)	6/15 (40%)
Studies on walkability only	7/12 (58%)	1/2 (50%)	3/9 (33%)

Number of significant cases/total number of cases.

However, these reviews mostly included cross-sectional studies and did not statistically assess the strength of the evidence using meta-analytical approaches that accounted for the methodological quality of the studies. Based on findings of the current review, it can be argued that living in more walkable and less-sprawled areas may provide residents with long-term benefits for cardio-metabolic health.

We found weak evidence for the relationships between neighbourhood recreational facilities and obesity outcomes. This implies that, to some extent, having more places in the neighbourhood to engage in moderate-to-vigorous physical activity may be protective against the development of obesity. No evidence was found for the relationships between access to green space or parks and obesity outcomes. This finding is in line with a previous systematic review of cross-sectional studies, which reported inconsistent findings for relationships between access to green space and obesity outcomes (74). It should be noted that studies on green spaces and cardiovascular health assuming a pathway other than physical activity (e.g. air quality and stress) were not included in the current review due to our inclusion criteria. Considering that researchers and practitioners consider POS as important and modifiable community resources that can contribute to resident's health (75), further longitudinal research on POS and health is warranted. It is known that the quality aspects of POS (size, features and amenities) are relevant to residents' walking to and active use of POS (76). Research may need to incorporate the quality of POS to examine how they are associated with cardio-metabolic health.

Other environmental measures (destinations, routes and other composite measures), for which we were able to synthesize findings, did not show any evidence of longitudinal relationships with obesity outcomes. Because the presence of local destinations is consistently associated with residents' walking (25,77,78), it was expected that residents of such locations would have lower risk of obesity. However, meta-analysis did not find any evidence for longitudinal relationships of access to local destinations with obesity outcomes. Because a large volume of walking (over 300 min week^{-1}) is needed to reduce obesity risk (79), walking to local proximate destinations may not be long enough. Several measures related to route aspects (street connectivity, traffic, safety and slope) were combined to carry out meta-analysis in this review. We found no evidence for the combined impact of such route characteristics on obesity outcomes. This may be because these route attributes differed in their associations with cardio-metabolic health outcomes. For example, neighbourhood traffic was found to be consistently associated with BMI increase (40), T2D incidence (52) and hypertension incidence (57), but neighbourhood safety was not associated with T2D incidence (47) or hypertension incidence (55). This review found a relatively large number of studies examining composite environmental measures, such as walkability and urban sprawl. However, less research has been carried out on specific environmental attributes (such as residential density and street connectivity). There is a need for further longitudinal studies to identify specific built environment attributes that affect health outcomes to inform future urban design guidelines for new and established communities.

With regard to the outcome variables, obesity was still the most prevalent health outcome in this review (58%). However, the current review found that more than one third of the articles examined other cardio-metabolic health outcomes such as T2D and hypertension outcomes. Research in exercise science has shown that active lifestyle changes can be effective in reducing the risk of T2D and hypertension and can improve cardio-metabolic health profiles, even when there is no effective change in adiposity (80). This suggests that environmental attributes found to have weak or no evidence of longitudinal relationships with obesity (recreational facilities, POS, destinations and routes) may be strongly or weakly related to T2D and hypertension outcomes. Future research needs to investigate about what aspects of built environments might be protective against broader cardio-metabolic diseases.

Issues on research design

Longitudinal studies of built environments involve either people who stayed in the same address (stayers) or those who relocated (movers). For studies on stayers, it is important to ensure that participants did not change their address during the study period. However, as shown in Table 1, many of the studies on stayers assumed that participants did not relocate or not explicitly reported about their relocation status. It is possible that the lower percentage of significant findings for assumed stayers (Table 4) may be due to the error introduced by including some participants who moved to a different neighbourhood during the study period.

Examining environmental changes is considered to provide useful knowledge. In most cases, studies on stayers are unlikely to be suitable for examining environmental changes, as any changes in established neighbourhoods are normally modest and slow. To better understand the health impact of significant environmental changes, research can use natural experiments (e.g. examining the effect of new transport infrastructure) or examine environmental changes among those who relocated. However, as shown in Table 4, the studies on movers had a lower percentage of significant findings compared with the studies on stayers. Some movers may have relocated not long before the follow-up measurement thus may have had only a limited exposure to the new environment. To accurately examine the effects of environmental changes among movers, the time of relocation is needed to identify how long participants were exposed to the old and new environments, but only one study

considered when during the study period participants relocated (44). This may be a reason for finding fewer significant results in the studies on movers.

Longer periods are considered beneficial for examining cardio-metabolic outcomes, because it takes time to develop these conditions (81). Data collection from multiple time points can be also advantageous, as it facilitates an examination of whether changes occurred consistently across time (82,83). The majority of the studies had follow-up periods of 5 years or longer, and many of these had data collection at three or more time points. However, longer follow-ups may also incur higher and systematic attrition, which can cause bias in the estimates (84). A quantitative comparison on key characteristics of those who dropped out to those who remained in the study can be helpful to identify systematic attrition and to account for it. Another issue with a longer follow-up is that some environmental attributes can change over a long period of time (e.g. loss/addition of destinations and new residential development). However, less than 20% of the studies in this review measured environmental attributes at the same time with outcome measures. It is important that environmental attributes were measured at multiple points concurrent with health data collection, even for studies on stayers.

Built environment measurement methods

Objective and perceived measures capture distinct aspects of the built environment (85). Mismatches between perceived and objectives measures of walkability attributes in the prospective relationships with BMI were reported previously (86). It was found that the strength of evidence for relationships between walkability and health outcomes was attenuated when the meta-analysis was restricted to objective measures of walkability, which suggests that perceived walkability may be more strongly related to health outcomes. It is possibly because of the match between participants' perceived local area and area where their daily behaviours take place. In contrast, objective walkability was assessed within a buffer area around the home or an administrative area, which may or may not match the area where participants' daily behaviours take place. Street-network buffers are considered as more likely to capture an accessible local area for residents, compared with alternative straight-line buffers or administrative units (87). However, less than a quarter of the studies reviewed employed street-network buffers. Similarly, buffer sizes also need to be appropriate for different types of attributes (e.g. POS compared with utilitarian destinations) (32) and for different subgroups (e.g. older adults compared with younger adults) (88). Not capturing local areas accurately in objective measures may have contributed to weakening the relevant evidence (89).

Residential self-selection

The relationship between built environment attributes and cardio-metabolic outcomes may be confounded by participants' self-selection of residential location (e.g. health conscious people chose to live in environments supportive of physical activity). If not appropriately adjusted, this may *magnify* the relationships between built environments and health outcomes (90). However, as shown in this review, cohort studies that are designed to collect health-related data do not often measure participants' attitudes about or preferences for residential location. In the absence of self-selection data, alternative analytical approaches (i.e. propensity score matching and fixed effects models) can be used (90) to address confounding due to residential self-selection as was done in some reviewed studies (43,44,46,49,52–54,67,68).

Mediation by physical activity

We postulated in this review that the relationships between built environment attributes and cardio-metabolic health outcomes are partly mediated by physical activity. However, we did not find conclusive evidence for mediation by physical activity, mainly due to limitations in traditional statistical mediation analysis that has been shown to provide incorrect findings (91). For example, traditional methods require that the total effect of an exposure on an outcome must be non-zero and larger than the direct effect, to observe a significant indirect effect. However, recent statistical mediation analysis literature argue that it is possible to have a non-significant total effect yet a significant indirect effect (i.e. when multiple mediating pathways exist and cancel out each other) (92). In relationships between built environment exposures and cardio-metabolic health outcomes, it is hypothesized that multiple mediating pathways exist (e.g. physical activity, dietary behaviours and air pollution) (9). Thus, care must be taken to disentangle the individual mediating mechanisms. In addition, when estimating the total effect of an exposure on an outcome, inappropriate adjustment for intermediate behavioural variables may lead to *overadjustment* and can produce incorrect null findings (93). Further, despite some increased attention in recent years to understand environmental correlates of sedentary behaviour, and the health impacts of daily sedentary behaviour such as TV viewing and car driving (94,95), no studies have examined how this behaviour is involved in longitudinal relationships between built environments and cardio-metabolic health. To better understand how environmental attributes influence residents' health, future studies need to examine the role of multiple potential behaviours using the recent developments in mediation analysis methods (73).

Strengths and limitations

The present systematic review has several strengths. We exclusively reviewed longitudinal studies by systematically searching eight databases. We assessed the methodological quality of the articles using a quality assessment tool that accounted for methodological issues including study design, measurement and analysis, and synthesized the evidence using meta-analysis. One of the limitations of this study is that the quality assessment tool, which was adapted from Cerin *et al*. (23), was extended mainly using inputs from the co-authors. A Delphi study aiming to obtain consensus among experts about key criteria for assessing quality in built environment and health studies can produce a more robust synthesis of the literature in future systematic reviews. We grouped exposure variables to succinctly summarize current knowledge. However, the reviewed studies varied in how environmental attributes were measured, and that variation may have influenced the summary findings shown in Table 3. In particular, the studies differed in calculating the composite index of walkability. Future research can explore further how different walkability indices are associated with health outcomes, to produce composite environmental measures that can better predict long-term impacts on cardio-metabolic health. This review focused on studies that examined the health impact of areas where participants resided, typically using a buffer or an administrative area around participant's residence. However, it is possible that environment outside such areas may also affect health. Future research/review can investigate the health impact of other specific environments, such as workplace (and its vicinity) and access to a regional centre. We may have missed some studies on greenness and cardio-metabolic health, because diverse research fields, using terms that were not included in search terms of this review (e.g. vegetation, land cover and forest), have investigated this topic. The presence of multiple pathways between greenspace and health made it difficult for this review to include all the studies on this topic in a realistic manner. A future review, focusing on greenspace yet incorporating multiple pathways, is needed to better understand the overall health benefits of greenspace. Most of the studies reviewed were conducted in a limited number of Western countries, which limits the generalizability of the findings to non-Western countries and to other developed/developing countries. Considering that developing countries may experience greater environmental changes in a shorter timeframe, further longitudinal studies from various parts of the world are needed.

Conclusion

The systematic review with meta-analysis of longitudinal studies found that living in more walkable and less-sprawled areas is likely to have protective effects against the development of obesity, T2D and hypertension. Future longitudinal studies need to examine relationships of specific attributes of built environments with a range of cardio-metabolic outcomes including T2D, hypertension and CVD. Research on behavioural mechanisms is also warranted to identify underlying behaviours involved in relationships between built environments and cardio-metabolic health.

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Conflict of interest statement

The authors report no conflicts of interest.

Author contributions

M. C. and T. S. conceived the study. All authors contributed to the initial planning of the review. M. C., J. R., L. G. and T. S. developed the search strategy. M. C. performed database searches. M. C., J. R. and L. G. independently screened titles and abstracts, read full articles and extracted data. T. S. mediated the discrepancies in article screening. M. C. and T. S. developed the quality assessment tool with inputs from all authors. M. C. assessed study quality and performed meta-analysis. M. C. and T. S. drafted the manuscript. All authors contributed to reviewing and revising the manuscript, read and approved the final manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
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Table S1. Search terms used
Table S2: Methodological Quality-Assessment Tool
Table S3: Summary of data extracted from reviewed articles
Table S4: Methodological quality and sample size assessment scores
Table S5: Complete meta-analysis results

References

1. Roth GA, Johnson C, Abajobir A *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017; **70**(1): 1–25.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; **87**(1): 4–14.
3. Fisher M. Cardiometabolic disease: the new challenge? *Practical Diabetes* 2006; **23**(3): 95–97.
4. Pearson TA, Blair SN, Daniels SR *et al*. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation* 2002; **106**(3): 388–391.
5. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**(6865): 782–787.
6. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. *Lancet* 2014; **384**(9937): 45–52.
7. Hallal PC, Andersen LB, Bull FC *et al*. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 2012; **380**(9838): 247–257.
8. Sallis JF, Floyd MF, Rodriguez DA, Saelens BE. Role of built environments in physical activity, obesity, and cardiovascular disease. *Circulation* 2012; **125**(5): 729–737.
9. Giles-Corti B, Vernez-Moudon A, Reis R *et al*. City planning and population health: a global challenge. *Lancet* 2016; **388**(10062): 2912–2924.
10. Black JL, Macinko J. Neighborhoods and obesity. *Nutr Rev* 2008; **66**(1): 2–20.
11. Booth KM, Pinkston MM, Poston WS. Obesity and the built environment. *J Am Diet Assoc* 2005; **105**(5 Suppl 1): S110–S117.
12. Durand CP, Andalib M, Dunton GF, Wolch J, Pentz MA. A systematic review of built environment factors related to physical activity and obesity risk: implications for smart growth urban planning. *Obes Rev* 2011; **12**(5): e173–e182.
13. Grasser G, Van Dyck D, Titze S, Stronegger W. Objectively measured walkability and active transport and weight-related outcomes in adults: a systematic review. *Int J Public Health* 2013; **58**(4): 615–625.
14. Leal C, Chaix B. The influence of geographic life environments on cardiometabolic risk factors: a systematic review, a methodological assessment and a research agenda. *Obes Rev* 2011; **12**(3): 217–230.
15. Mackenbach JD, Rutter H, Compernolle S *et al*. Obesogenic environments: a systematic review of the association between the physical environment and adult weight status, the SPOTLIGHT project. *Bmc Public Health* 2014; **14**(1): 233.
16. Malambo P, Kengne AP, De Villiers A, Lambert EV, Puoane T. Built environment, selected risk factors and major cardiovascular disease outcomes: a systematic review. *PLoS One* 2016; **11**(11): e0166846.
17. Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. The built environment and obesity. *Epidemiol Rev* 2007; **29**: 129–143.
18. Owen N, Leslie E, Salmon J, Fotheringham MJ. Environmental determinants of physical activity and sedentary behavior. *Exerc Sport Sci Rev* 2000; **28**(4): 153–158.
19. Sallis JF, Owen N. Ecological models of health behavior. In: Glanz K, Rimer BK, Viswanath K (eds). Health Behavior: Theory, Research, and Practice. Jossey-Bass: San Francisco, 2015, pp. 43–64.
20. Marteau TM, Hollands GJ, Fletcher PC. Changing human behavior to prevent disease: the importance of targeting automatic processes. *Sci* 2012; **337**(6101): 1492–1495.
21. Aadahl M, Kjaer M, Jorgensen T. Associations between overall physical activity level and cardiovascular risk factors in an adult population. *Eur J Epidemiol* 2007; **22**(6): 369–378.
22. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. *Int J Epidemiol* 2012; **41**(5): 1338–1353.
23. Cerin E, Nathan A, van Cauwenberg J *et al*. The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis. *Int J Behav Nutr Phys Act* 2017; **14**(1): 15.
24. Koohsari MJ, Sugiyama T, Sahlqvist S, Mavoa S, Hadgraft N, Owen N. Neighborhood environmental attributes and adults' sedentary behaviors: review and research agenda. *Prev Med* 2015; **77**: 141–149.
25. Sugiyama T, Neuhaus M, Cole R, Giles-Corti B, Owen N. Destination and route attributes associated with adults' walking: a review. *Med Sci Sports Exerc* 2012; **44**(7): 1275–1286.
26. Van Cauwenberg J, De Bourdeaudhuij I, De Meester F *et al*. Relationship between the physical environment and physical activity in older adults: a systematic review. *Health place* 2011; **17**(2): 458–469.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(7): e1000097.
28. Thorp AA, Owen N, Neuhaus M, Dunstan DW. Sedentary behaviors and subsequent health outcomes in adults a systematic review of longitudinal studies, 1996–2011. *Am J Prev Med* 2011; **41**(2): 207–215.
29. Ding D, Gebel K. Built environment, physical activity, and obesity: what have we learned from reviewing the literature? *Health Place* 2012; **18**(1): 100–105.
30. Barnett DW, Barnett A, Nathan A *et al*. Built environmental correlates of older adults' total physical activity and walking: a systematic review and meta-analysis. *Int J Behav Nutr Phys Act* 2017; **14**(1): 103.
31. Tooth L, Ware R, Bain C, Purdie DM, Dobson A. Quality of reporting of observational longitudinal research. *Am J Epidemiol* 2005; **161**(3): 280–288.
32. Giles-Corti B, Gunn L, Hooper P *et al*. Built environment and physical activity. In: Nieuwenhuijsen M, Khreis H (eds). Integrating Human Health into Urban and Transport Planning. Springer: Cham, 2019.
33. Whitlock MC. Combining probability from independent tests: the weighted Z-method is superior to Fisher's approach. *J Evol Biol* 2005; **18**(5): 1368–1373.
34. Bland M. An Introduction to Medical Statistics. Oxford University Press: UK, 2015.
35. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009; **172**(1): 137–159.
36. Albrecht SS, Osypuk TL, Kandula NR *et al*. Change in waist circumference with longer time in the United States among Hispanic and Chinese immigrants: the modifying role of the neighborhood built environment. *Ann Epidemiol* 2015; **25**(10): 767–772 e2.
37. Arcaya M, James P, Rhodes JE, Waters MC, Subramanian SV. Urban sprawl and body mass index among displaced Hurricane Katrina survivors. *Prev Med* 2014; **65**: 40–46.
38. Auchincloss AH, Diez Roux AV, Mujahid MS, Shen M, Bertoni AG, Carnethon MR. Neighborhood resources for physical activity and healthy foods and incidence of type 2 diabetes mellitus: the

multi-ethnic study of atherosclerosis. *Arch Intern Med* 2009; **169**(18): 1698–1704.
39. Auchincloss AH, Mujahid MS, Shen M, Michos ED, Whitt-Glover MC, Diez Roux AV. Neighborhood health-promoting resources and obesity risk (the multi-ethnic study of atherosclerosis). *Obesity (Silver Spring)* 2013; **21**(3): 621–628.
40. Berry TR, Spence JC, Blanchard C, Cutumisu N, Edwards J, Nykiforuk C. Changes in BMI over 6 years: the role of demographic and neighborhood characteristics. *Int J Obes (Lond)* 2010; **34**(8): 1275–1283.
41. Berry TR, Spence JC, Blanchard CM, Cutumisu N, Edwards J, Selfridge G. A longitudinal and cross-sectional examination of the relationship between reasons for choosing a neighbourhood, physical activity and body mass index. *Int J Behav Nutr Phys Act* 2010; **7**: 57.
42. Boone-Heinonen J, Diez-Roux AV, Goff DC *et al*. The neighborhood energy balance equation: does neighborhood food retail environment + physical activity environment = obesity? The CARDIA study. *PLoS One* 2013; **8**(12): e85141.
43. Booth GL, Creatore MI, Moineddin R *et al*. Unwalkable neighborhoods, poverty, and the risk of diabetes among recent immigrants to Canada compared with long-term residents. *Diabetes Care* 2013; **36**(2): 302–308.
44. Braun LM, Rodriguez DA, Evenson KR, Hirsch JA, Moore KA, Diez Roux AV. Walkability and cardiometabolic risk factors: cross-sectional and longitudinal associations from the multi-ethnic study of atherosclerosis. *Health Place* 2016; **39**: 9–17.
45. Calling S, Li X, Kawakami N, Hamano T, Sundquist K. Impact of neighborhood resources on cardiovascular disease: a nationwide six-year follow-up. *BMC Publ Health* 2016; **16**: 634.
46. Chiu M, Rezai MR, Maclagan LC *et al*. Moving to a highly walkable neighborhood and incidence of hypertension: a propensity-score matched cohort study. *Environ Health Perspect* 2016; **124**(6): 754–760.
47. Christine PJ, Auchincloss AH, Bertoni AG *et al*. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis (MESA). *JAMA Intern Med* 2015; **175**(8): 1311–1320.
48. Coogan PF, White LF, Evans SR *et al*. Longitudinal assessment of urban form and weight gain in African-American women. *Am J Prev Med* 2011; **40**(4): 411–418.
49. Griffin BA, Eibner C, Bird CE *et al*. The relationship between urban sprawl and coronary heart disease in women. *Health Place* 2013; **20**: 51–61.
50. Halonen JI, Kivimaki M, Pentti J *et al*. Green and blue areas as predictors of overweight and obesity in an 8-year follow-up study. *Obesity (Silver Spring)* 2014; **22**(8): 1910–1917.
51. Hamano T, Kawakami N, Li X, Sundquist K. Neighbourhood environment and stroke: a follow-up study in Sweden. *PLoS One* 2013; **8**(2): e56680.
52. Heidemann C, Niemann H, Paprott R, Du Y, Rathmann W, Scheidt-Nave C. Residential traffic and incidence of type 2 diabetes: the German Health Interview and Examination Surveys. *Diabet Med* 2014; **31**(10): 1269–1276.
53. Hirsch JA, Diez Roux AV, Moore KA, Evenson KR, Rodriguez DA. Change in walking and body mass index following residential relocation: the multi-ethnic study of atherosclerosis. *Am J Public Health* 2014; **104**(3): e49–e56.
54. Hirsch JA, Moore KA, Barrientos-Gutierrez T *et al*. Built environment change and change in BMI and waist circumference: multi-ethnic study of atherosclerosis. *Obesity (Silver Spring)* 2014; **22**(11): 2450–2457.
55. Kaiser P, Diez Roux AV, Mujahid M *et al*. Neighborhood environments and incident hypertension in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2016; **183**(11): 988–997.
56. Kawakami N, Li X, Sundquist K. Health-promoting and health-damaging neighbourhood resources and coronary heart disease: a follow-up study of 2 165 000 people. *J Epidemiol Community Health* 2011; **65**(10): 866–872.
57. Kingsley SL, Eliot MN, Whitsel EA *et al*. Residential proximity to major roadways and incident hypertension in post-menopausal women. *Environ Res* 2015; **142**: 522–528.
58. Lee IM, Ewing R, Sesso HD. The built environment and physical activity levels: the Harvard Alumni Health Study. *Am J Prev Med* 2009; **37**(4): 293–298.
59. Li F, Harmer P, Cardinal BJ *et al*. Built environment and 1-year change in weight and waist circumference in middle-aged and older adults: Portland Neighborhood Environment and Health Study. *Am J Epidemiol* 2009; **169**(4): 401–408.
60. Li F, Harmer P, Cardinal BJ, Vongjaturapat N. Built environment and changes in blood pressure in middle aged and older adults. *Prev Med* 2009; **48**(3): 237–241.
61. Michael YL, Gold R, Perrin N, Hillier TA. Built environment and change in body mass index in older women. *Health Place* 2013; **22**: 7–10.
62. Michael YL, Nagel CL, Gold R, Hillier TA. Does change in the neighborhood environment prevent obesity in older women? *Soc Sci Med* 2014; **102**: 129–137.
63. Paquet C, Coffee NT, Haren MT *et al*. Food environment, walkability, and public open spaces are associated with incident development of cardio-metabolic risk factors in a biomedical cohort. *Health Place* 2014; **28**: 173–176.
64. Plantinga AJ, Bernell S. The association between urban sprawl and obesity: is it a two-way street? *J Reg Sci* 2007; **47**(5): 857–879.
65. Sarkar C, Gallacher J, Webster C. Built environment configuration and change in body mass index: the Caerphilly Prospective Study (CaPS). *Health Place* 2013; **19**: 33–44.
66. Sundquist K, Eriksson U, Mezuk B, Ohlsson H. Neighborhood walkability, deprivation and incidence of type 2 diabetes: a population-based study on 512,061 Swedish adults. *Health Place* 2015; **31**: 24–30.
67. Tamosiunas A, Grazuleviciene R, Luksiene D *et al*. Accessibility and use of urban green spaces, and cardiovascular health: findings from a Kaunas cohort study. *Environ Health* 2014; **13**(1): 20.
68. Wasfi RA, Dasgupta K, Orpana H, Ross NA. Neighborhood walkability and body mass index trajectories: longitudinal study of Canadians. *Am J Public Health* 2016; **106**(5): 934–940.
69. Braun LM, Rodriguez DA, Song Y *et al*. Changes in walking, body mass index, and cardiometabolic risk factors following residential relocation: longitudinal results from the CARDIA study. *J Transp Health* 2016; **3**(4): 426–439.
70. Sugiyama T, Niyonsenga T, Howard NJ *et al*. Residential proximity to urban centres, local-area walkability and change in waist circumference among Australian adults. *Prev Med* 2016; **93**: 39–45.
71. Carroll SJ, Niyonsenga T, Coffee NT, Taylor AW, Daniel M. Does physical activity mediate the associations between local-area descriptive norms, built environment walkability, and glycosylated hemoglobin? *Int J Environ Res Publ Health* 2017; **14**(9): 953.
72. Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. Relationship between urban sprawl and physical activity, obesity, and morbidity. *Am J Health Promot* 2003; **18**(1): 47–57.
73. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health* 2016; **37**: 17–32.

74. Lachowycz K, Jones AP. Greenspace and obesity: a systematic review of the evidence. *Obes Rev* 2011; **12**(5): e183–e189.
75. Stankov I, Howard NJ, Daniel M, Cargo M. Policy, research and residents' perspectives on built environments implicated in heart disease: a concept mapping approach. *Int J Environ Res Public Health* 2017; **14**(2): 170.
76. Sugiyama T, Gunn LD, Christian H *et al*. Quality of public open spaces and recreational walking. *Am J Public Health* 2015; **105**(12): 2490–2495.
77. Glazier RH, Creatore MI, Weyman JT *et al*. Density, destinations or both? A comparison of measures of walkability in relation to transportation behaviors, obesity and diabetes in Toronto, Canada. *PLoS One* 2014; **9**(1): e85295.
78. Cole R, Dunn P, Hunter I, Owen N, Sugiyama T. Walk Score and Australian adults' home-based walking for transport. *Health Place* 2015; **35**: 60–65.
79. Fogelholm M. Walking for the management of obesity. *Dis Manag Health Out* 2005; **13**(1): 9–18.
80. Gaesser GA, Angadi SS, Sawyer BJ. Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. *Phys Sportsmed* 2011; **39**(2): 87–97.
81. Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity – a systematic review of longitudinal studies. *BMC Publ Health* 2013; **13**(1): 813.
82. Rogosa D. Myths and methods:"myths about longitudinal research" plus supplemental questions. In: The Analysis of Change, Vol. **3**, 1995, p. 66.
83. Taris TW. A Primer in Longitudinal Data Analysis. Sage: London, 2000.
84. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2003; **19**(8): 751–760.
85. Orstad SL, McDonough MH, Stapleton S, Altincekic C, Troped PJ. A systematic review of agreement between perceived and objective neighborhood environment measures and associations with physical activity outcomes. *Environ Behav* 2017; **49**(8): 904–932.
86. Gebel K, Bauman AE, Sugiyama T, Owen N. Mismatch between perceived and objectively assessed neighborhood walkability attributes: prospective relationships with walking and weight gain. *Health Place* 2011; **17**(2): 519–524.
87. James P, Berrigan D, Hart JE *et al*. Effects of buffer size and shape on associations between the built environment and energy balance. *Health Place* 2014; **27**: 162–170.
88. Villanueva K, Knuiman M, Nathan A *et al*. The impact of neighborhood walkability on walking: does it differ across adult life stage and does neighborhood buffer size matter? *Health Place* 2014; **25**: 43–46.
89. Kwan MP. The uncertain geographic context problem. *Ann. Assoc. Am. Geogr* 2012; **102**(5): 958–968.
90. Boone-Heinonen J, Gordon-Larsen P, Guilkey DK, Jacobs DR Jr, Popkin BM. Environment and physical activity dynamics: the role of residential self-selection. *Psychol Sport Exerc* 2011; **12**(1): 54–60.
91. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *Int J Epidemiol* 2013; **42**(5): 1511–1519.
92. Mascha EJ, Dalton JE, Kurz A, Saager L. Statistical grand rounds: understanding the mechanism: mediation analysis in randomized and nonrandomized studies. *Anesth Analg* 2013; **117**(4): 980–994.
93. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiol* 2009; **20**(4): 488–495.
94. Pereira SMP, Ki M, Power C. Sedentary behaviour and biomarkers for cardiovascular disease and diabetes in mid-life: the role of television-viewing and sitting at work. *PLoS One* 2012; **7**(2): e31132.
95. Sugiyama T, Wijndaele K, Koohsari MJ, Tanamas SK, Dunstan DW, Owen N. Adverse associations of car time with markers of cardio-metabolic risk. *Prev Med* 2016; **83**: 26–30.

2.3 Research Gaps Identified in the Systematic Review

The systematic review with meta-analysis found strong evidence for potential long-term impacts of some built environment attributes on cardio-metabolic health outcomes. Living in high walkable neighbourhoods, in particular, was found to be linked to lower cardio-metabolic risk over time. The systematic review highlighted a number of research gaps, which are summarised below.

2.3.1 Outcome measures

A majority of existing longitudinal studies identified in the systematic review examined obesity-related outcomes (60%), with a relatively smaller portion of the studies examining hypertension (20%) and T2D (25%) related outcomes. However, they were mostly examined as events (i.e., incidences of hypertension or T2D). Investigating continuous changes in the markers of cardio-metabolic risk is important to better understand the potential population-level health impacts of built environments. Also, other cardio-metabolic risk factors (e.g., dyslipidaemia) were less examined in the studies reviewed.

2.3.2 Exposure measures

A majority of studies reviewed examined composite indices of built environment attributes (e.g., walkability). There has been limited research examining specific built environment attributes. Over 80% of the studies identified in the systematic review measured built environment attributes at one point in time (often at baseline). Given that neighbourhood built environments can change over time and the degree of such changes may differ between localities (51, 52), it is of interest to investigate the relationships between changes in built environmental attributes and changes in cardio-metabolic risk. Further, most of the existing longitudinal studies used predefined administrative units to define neighbourhoods, which may not accurately capture residents' accessible local areas (53).

2.3.3 The role of physical activity

The systematic review reported inconclusive findings for the potential mediating role of physical activity in the relationships between the built environment and cardio-metabolic health. It was observed that inappropriate analytical methods were used for assessing

mediation, despite that new mediation analysis methods have been developed over the last two decades (54). Thus, it is important to employ recent developments in mediation analysis to better assess the role of physical activity in the relationships between the built environment and cardio-metabolic health. In particular, although there is evidence for potential long-term beneficial impacts of walkability on cardio-metabolic health, the role of physical activity in those relationships is less clear. Further, physical activity levels can change over time. Mediation analysis examining physical activity changes can also be informative.

2.3.4 Lack of Australian studies with multiple sites

The systematic review identified that a majority of studies had participants recruited from multiple sites, but most of those studies were conducted in the USA. All three Australian articles reviewed were based on the North West Adelaide Health Study, which recruited participants from a single site (the north-western metropolitan region of Adelaide). Investigating multiple sites across Australia is important to increase the variability of environmental attributes and the generalisability of the findings in the Australian context.

2.4 Specific Research Questions for Empirical Studies

Two empirical studies were designed to address the research gaps discussed above. The first empirical study (referred to as **Study Two**, reported in Chapter 4) examined the impacts of changes in a specific built environment attribute (i.e., population density increase) on changes in multiple cardio-metabolic risk markers among Australian adults. The second empirical study (referred to as **Study Three**, reported in Chapter 5) investigated the potential mediating role physical activity in the relationship between walkability and changes in multiple cardio-metabolic risk markers among Australian adults. Figures 2.1 and 2.2 illustrate the relationships examined in Study Two and Study Three, respectively. Both studies used data collected from multiple sites in Australia.

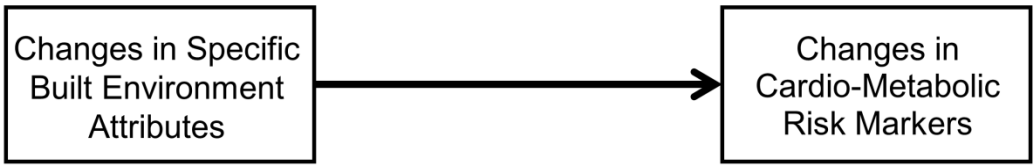


Figure 2.1: Conceptual Model for Study Two

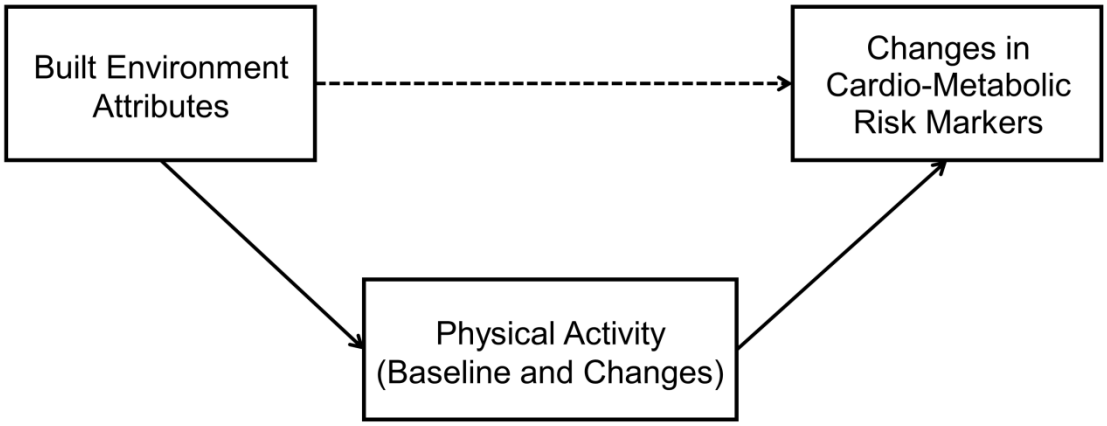


Figure 2.2: Conceptual Model for Study Three

CHAPTER 3: METHODS

This Chapter explains the data used and the methods employed in the two empirical studies. More specifically, it describes the following four topics: (1) data collection methods of the AusDiab study; (2) calculation of built environment attributes for the AusDiab study participants; (3) description of the analytical sample and specific variables used; and (4) statistical analyses.

3.1 The Australian Diabetes, Obesity and Lifestyle Study

3.1.1 Background

The empirical studies of this Thesis were conducted using data from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. The AusDiab study is the first Australian national cohort study examining the prevalence, incidence and risk factors of diabetes and cardiovascular disease among Australian adults. The AusDiab study commenced in 1999–2000 with the baseline data collection (AusDiab1), had a 5-year follow-up data collection in 2004–2005 (AusDiab2), and a 12-year follow-up data collection in 2011–12 (AusDiab3). The International Diabetes Institute and Alfred Hospital Ethics Committee provided ethics approvals for the AusDiab study (# 39/11). The details of the AusDiab study were previously described by Dunstan et al. (55) and in the three reports published after each data collection (56-58). The following subsections describe the details of the AusDiab study methods relevant to this Thesis.

3.1.2 Study areas and recruitment of participants

The inclusion criteria for the AusDiab1 sample recruitment were non-institutionalised adults aged over 25 years, without any physical or intellectual disabilities, and residing in private dwellings for a minimum of six months prior to data collection. The minimum sample size was determined to be 10,500, to provide a precise estimate of the national diabetes prevalence rate of 7% (95% CI: 6.2-7.8) at the time of AusDiab1.

A two-stage stratified cluster sampling method was used to recruit study participants. Within each of six states and the Northern Territory of Australia, six study areas in metropolitan and regional cities were selected to give a total of 42 study areas. Study areas consisted of up to four contiguous Census Collector District (CCD) geographical units. A CCD was the smallest geographical unit for census data collection (averaging approximately 225 dwellings) at the time of AusDiab1 (59). Any CCDs that met any of the following were excluded:

- fewer than 100 adults over 25 years;
- defined as 100% rural according to the 1996 Australian census;
- contained more than 10% indigenous population (to avoid the bias of having CCDs with an unrepresentative number of people with diabetes);
- defined predominantly an industrial/business zone;
- no eligible 'neighbouring' CCDs; and
- involved in a large-scale diabetes-related health survey recent to the time of the baseline.

Initially, six CCDs were randomly selected from eligible CCDs with a selection probability proportional to the size of population aged 25+ years from each state and territory. Then, to meet the minimum sample size threshold for each study area (i.e., 10,500/42 = 250) within the logistic and economic constraints, each original CCD was supplemented with contiguous neighbouring CCDs when required. Three study areas comprised single CCDs, 22 study areas comprised pairs of CCDs, 16 study areas comprised triplets of CCDs, and one study area comprised a quartet of CCDs. Figure 3.1 shows the locations of the study areas. The names of the administrative areas that contain study areas are listed in Table 3.1.

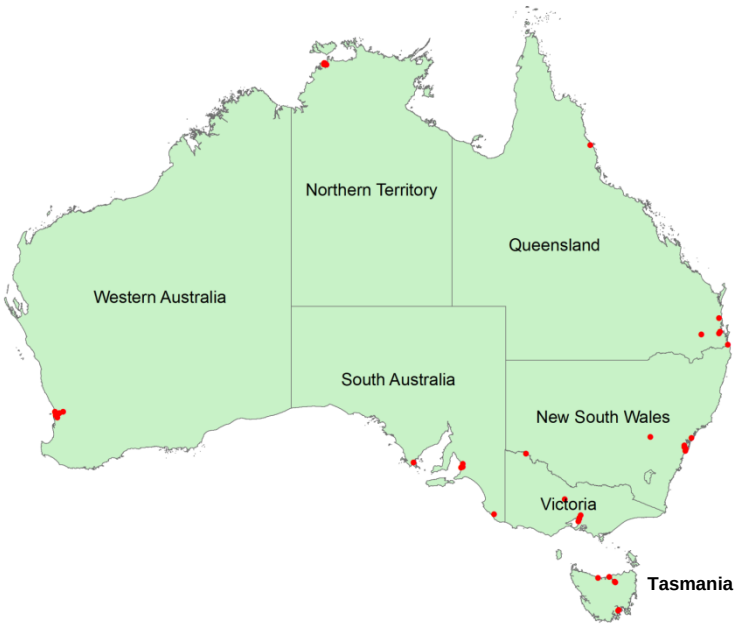


Figure 3.1: Locations of the AusDiab Study Areas

Table 3.1: The List of Administrative Areas containing the AusDiab Study Areas

State / territory	**Administrative Areas**
New South Wales (NSW)	West Pennant Hills, Hurstville, Auburn, Grays Point, Orange, Berkeley Vale
Northern Territory (NT)	Driver, Marrara, Nightcliff, Wagaman, Larrakeyah, Parap
Queensland (QLD)	Cairns, Chapel Hill, Nambour, East Toowoomba, Stafford Heights, Currumbin
South Australia (SA)	Hyde Park, Netley, Glenelg, Port Lincoln, Millicent, Parafield Gardens
Tasmania (TAS)	Alanvale, Ravenswood, Georgetown, Ulverstone, Taroona, Blackmans Bay
Victoria (VIC)	Parkdale, Blackburn North, Burwood East. Wattle Glen, Bendigo, Mildura
Western Australia (WA)	Trigg, Scarborough, Kardinya, High Wycombe, Mt Helena, Oakford

The baseline data collection was conducted between May 1999 and December 2000. In all study areas, following local media campaigns, a letter and a brochure that provided

information about the AusDiab study were hand-delivered to all private dwellings. Following this, AusDiab interviewers approached 25,984 households from which 20,347 people were identified as being eligible to participate in the study. Of these, 11,247 people participated in the baseline biomedical data collections by attending a testing site located within each study area. The baseline response rate (for biomedical examinations) was 55.3% (= 11,247/20,347). Figure 3.2 shows the flowchart of baseline participant recruitment.

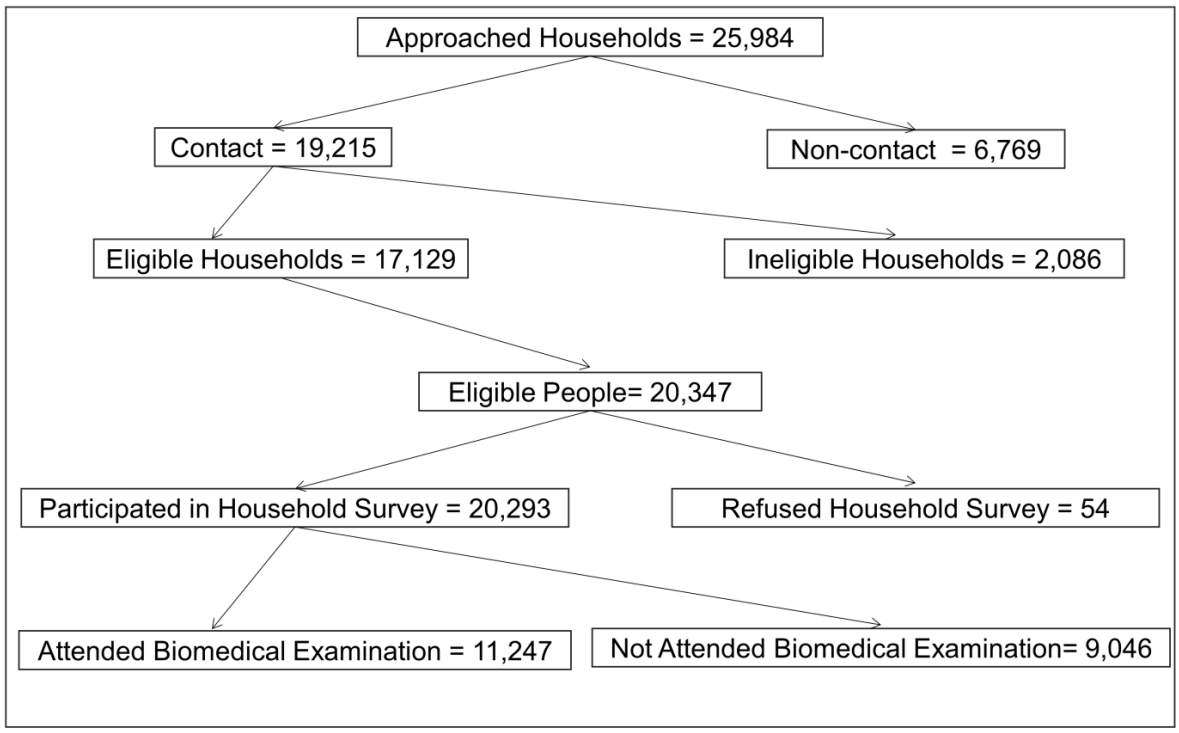


Figure 3.2: Flowchart for AusDiab1 Participant Recruitment
[Adapted from Dunstan et al., 2002 (55)]

3.1.3 The 5-year follow-up data collection (AusDiab2)

The 5-year follow-up data collection of the AusDiab study (AusDiab2) was conducted between June 2004 and December 2005. All eligible study participants were invited to the follow-up. Of the 11,247 AusDiab1 participants, 10,937 were identified as eligible for participation to AusDiab2. Of these, 6,400 participants attended for biomedical examinations, yielding a follow-up rate of 58.5%. Figure 3.3 shows a flowchart of AusDiab2 participant recruitment. The AusDiab study coordinators maintained an up-to-date database of study participants' addresses to maximise participation in the follow-up

surveys. This database was updated annually using a range of resources including next-of-kin, the Australian electoral roll database, White Pages® directory, and other online telephone directories. As some study participants had changed their residence between AusDiab1 and AusDiab2, one additional testing site was added in the Australian Capital Territory (Canberra), totalling 43 testing sites in AusDiab2.

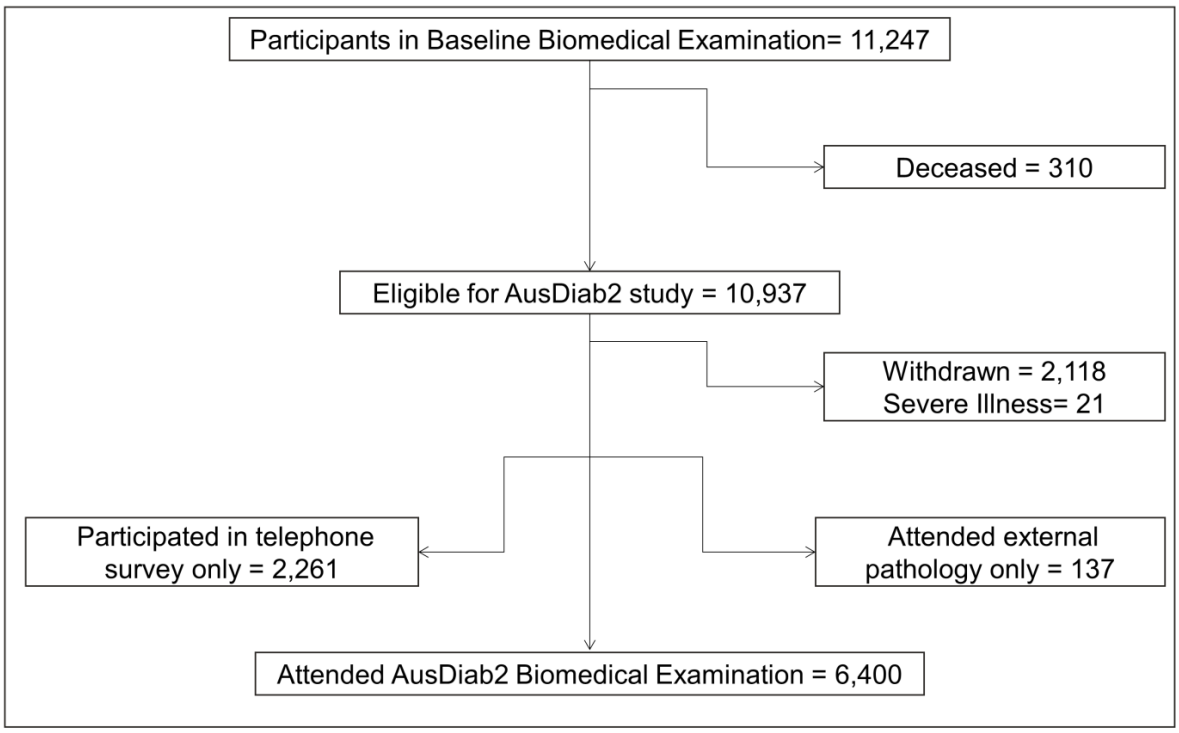


Figure 3.3: Flowchart for AusDiab2 Participant Recruitment
[Adapted from AusDiab Report 2005 (57)]

3.1.4 The 12-year follow-up data collection (AusDiab3)

The 12-year follow-up data collection of the AusDiab study (AusDiab3) was conducted between August 2011 and June 2012. All eligible study participants, including those who did not participate in AusDiab2, were invited to the 12-year follow-up. Of the 11,247 AusDiab1 participants, 10,337 were identified as eligible for participation to AusDiab3. Of these, 4,614 participants attended for biomedical examinations, yielding a follow-up rate of 44.6%. Figure 3.4 shows the flowchart of AusDiab3 participant recruitment. AusDiab3 had 46 testing sites (four additional sites as compared to AusDiab1), due to relocations of participants after AusDiab2.

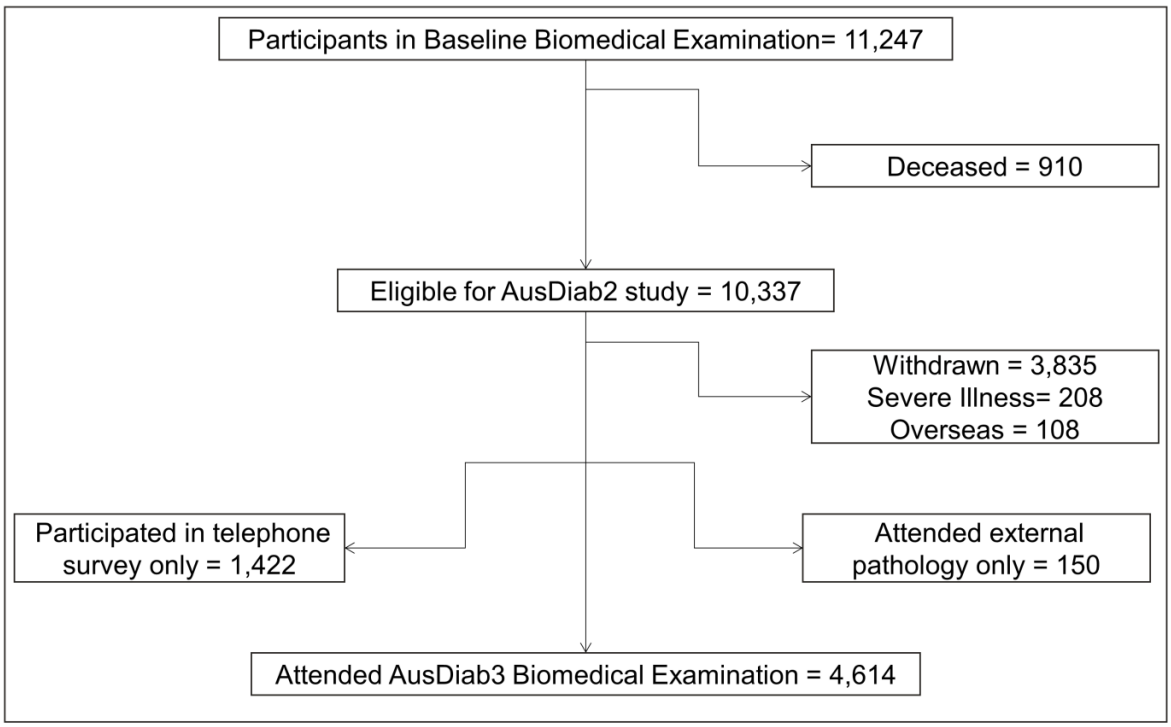


Figure 3.4: Flowchart for AusDiab3 Participant Recruitment
[Adapted from AusDiab Report 2012 (58)]

3.1.5 Data collection procedures

At each data collection of the AusDiab study, all eligible participants were invited to attend a local testing site for biomedical examinations and completion of a series of questionnaires. All study participants gave informed consent to participate in the study upon arrival at the testing site. The biomedical data collected were: blood samples after an overnight fast; anthropometric measures; blood pressure measures; morning spot urine samples; and blood sample after a 2-hour oral glucose tolerance test (OGTT). A series of interviewer-administered and self-administrated questionnaires were used to collect information such as participants' demographics, socio-economic status, lifestyle factors, and self-reported health status. Relevant details of the instruments used to measure the variables used in this Thesis are provided in section 3.3.

3.2 Built Environment Data for the AusDiab Study Participants

The AusDiab study was not primarily designed to examine the health impacts of built environments. To investigate such impacts, environmental data calculated for each

participant were linked to AusDiab individual data. This process started in 2014 as a subproject of the AusDiab study undertaken by the Centre for Research Excellence (CRE) in Healthy, Liveable Communities, of which the candidate is a member. This subproject focused on calculating built environment attributes for AusDiab3 participants. The candidate expanded the work of the CRE team by calculating new environmental measures at the time of AusDiab1 and AusDiab2 and additional environmental measures for AusDiab3. The following subsections describe the process of calculating environmental attributes using Geographic Information Systems (GIS) (60). This was an original work of this Thesis undertaken by the candidate with guidance from GIS experts in the CRE team. A flow chart outlining the process of calculating environmental attributes is provided in Appendix III (AIII.1).

3.2.1 Identifying eligible participants and their residential addresses

The Baker Heart and Diabetes Institute maintained an up-to-date residential addresses database of AusDiab study participants. However, participants' addresses corresponding to each of the three data collection time points were unavailable in a single database. The candidate, with the help of researchers who were involved in previous AusDiab studies, gathered participants' addresses data files corresponding to each data collection time point. As noted before, some participants had changed their residences during the study period, but their relocation dates were unavailable. Thus, it was decided not to include those who relocated (movers) in the empirical studies, as it was not possible to identify for how long they were exposed to different neighbourhoods within the 12-year study period. The empirical studies of this Thesis focused on those who stayed in the same address during the study period (stayers).

In processing participants' address data, a number of security procedures were adopted to protect the identity of AusDiab study participants. A protocol explaining these security procedures is provided in Appendix III (AIII.2).

3.2.2 Geocoding participants' residential addresses

Geocoding (i.e., converting text description of an address into geographic coordinates) of participants' residential addresses was the first step to calculate environmental attributes for each participant. It was initially done using *Geocoding toolbox* of the ArcGIS v.10.6 (ESRI, Redlands, CA) software. This process requires an appropriate reference file to look up and match an address to retrieve its geographic coordinates. The Geocoded National Address File (G-NAF) supplied by PSMA Australia was used for this purpose. The G-NAF is an authoritative list of physical addresses in Australia, being published since 2004. The geocoding hit rate (proportion of records that were geocoded) was 85% when both the G-NAF (the 2012 release) was used. To complement the initial process, Google Maps Geocoding Application Programming Interface (API) (61) was used as the second geocoding method. This method extracted longitude and latitude from Google maps, using a location query in an R software package 'ggmap' v.2.7.9. The geocoding hit rate was 98% in the second method. For the purpose of validation, geocoded results obtained from the two methods (G-NAF and Google Maps API) were compared. This was done by calculating the straight-line distances between the locations obtained using the two methods. If they were at least 100m apart, it was considered as a geocoding error (62). For 115 addresses that met this criterion, a third geocoding method, Bing Maps REST Services using a JavaScript (63), was applied. The geocode (G-NAF or Google Maps API methods) closer to the one obtained from the Bing Maps method was used for the subsequent calculation.

3.2.3 Creating buffers around the participant's residential address

In the empirical studies of this Thesis, neighbourhoods were operationalised as 'buffers' around participants' home addresses geocoded in GIS. Straight-line buffer (i.e., Euclidean or circular buffer) and street-network buffer are two commonly used buffers to define neighbourhoods in the neighbourhood and health research (53). A straight-line buffer places a circular area with a specific radius around the participant's home location (Figure 3.5 [a]). The *Buffer* tool in ArcGIS was used to create straight-line buffers. A street-network (sausage-type) buffer contains an area that can be reached within a specific distance along streets from the home with a certain bandwidth from the street centre line (Figure 3.5 [b]). The road network data from PSMA Australia's Transport & Topography

dataset (the 2012 release) was used for creating street-network buffers. Pedestrian non-accessible roads (e.g., expressways, freeways, motorways) were removed by filtering out those roads using "transport hierarchy codes" assigned to each road segment. Tools in *Network Analyst Extension* in ArcGIS were used to create street-network buffers. Straight-line buffers were used in Study Two (Chapter 4) and street-network buffers (sausage-type) were used in Study Three (Chapter 5). The rationales for the use of two different buffer types are provided in the respective chapters.

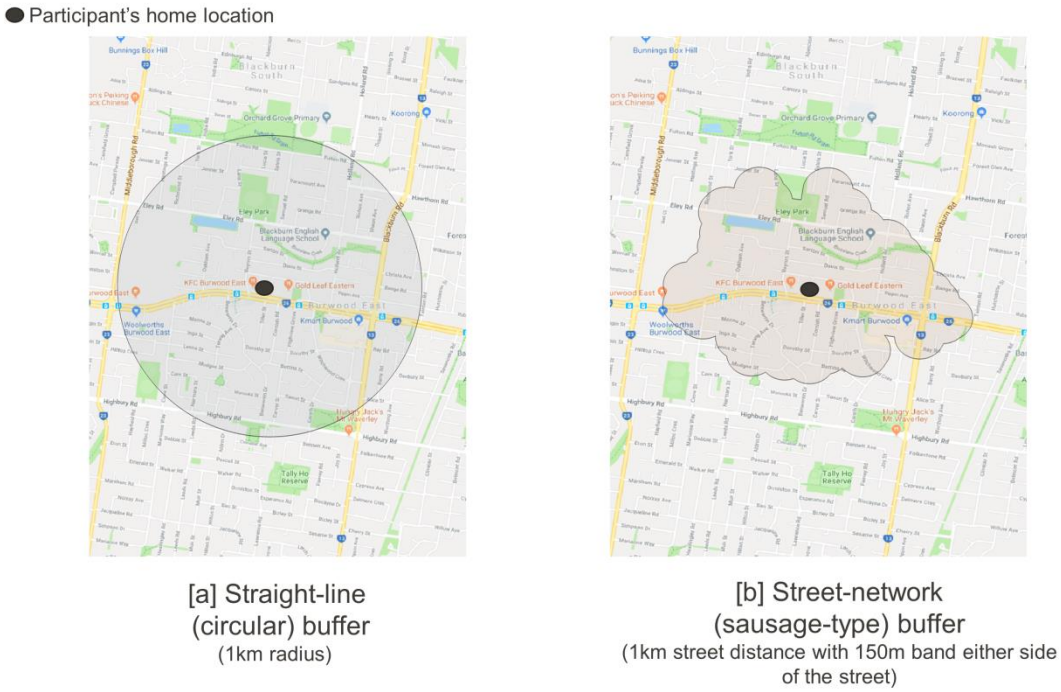


Figure 3.5: Straight-line Buffer and Street-network Buffer

For both types of buffers, 400-m, 1-km, 1.6-km distance buffers were created and built environmental attributes were calculated within each buffer. However, only those attributes within straight-line buffers of 1-km radius and street-network buffer of 1-km distance with 150-m band either side of the street centre line (64) were used in the corresponding empirical studies due to a large volume of analyses conducted in these studies. The distance of 1 km was chosen because it was shown to be a typical distance that adults walk to get to local destinations (65).

3.2.4 Calculating built environment attributes

Environmental attributes can be calculated once buffers are drawn around the geocode. Table 3.2 shows the list of built environmental attributes calculated in this Thesis with the source data used and their correspondence to AusDiab data collection time points. Measurement methods for each of them are described in the following subsections.

Table 3.2: Details of Built Environmental Attributes Calculated as Part of this Thesis

Built environment attributes	Geospatial data source	Source data corresponding to		
		AusDiab1	AusDiab2	AusDiab3
Population density†	Census	✓	✓	✓
Residential density*	Census		✓	✓
Intersection density (street connectivity)*	PSMA Australia (Transport & Topography)			✓
Destinations density*				✓
Supermarkets	Supermarkets, Pitney Bowes Ltd			✓
Convenience stores	Axiom Business Points, Pitney Bowes Ltd			✓
Train stations	PSMA Australia (Transport & Topography)			✓
Bus and tram stops	www.transitfeeds.com			✓
Parks (count, area, proximity)	PSMA Australia (Greenspace)		✓	
PedShed ratio	PSMA Australia (Transport & Topography)			✓
Street-network distance to the city centre	PSMA Australia (Transport & Topography)			✓
Walk Score®	www.walkscore.com			2016+

Note: † used in Study Two (Chapter 4), * used in Study Three (Chapter 5)

3.2.4.1 *Population and residential densities*

Population or residential densities are defined as the number of inhabitants or dwellings in the neighbourhood divided by its area, respectively (28). Australian Census (the national Census of Population and Housing) data collected by the Australian Bureau of Statistics (ABS) were used to calculate population and residential densities (66, 67). Census, which held in 2001, 2006, and 2011, align with the three AusDiab study data collection periods. The ABS releases population and dwellings count data for the smallest building blocks (without gaps or overlap) covering all Australia. In the 2001 Census, a Census Collection District (CCD) was the smallest building block and only the population count data were available. In the 2006 and 2011 Census, a Mesh Block (MB) was the smallest building block, and both population and dwellings count data were available. The total population/dwellings count for a buffer was calculated by summing the respective counts of the Census units included in the buffer. If the buffer intersected a Census unit, that unit's count corresponding to the percentage of the area within the buffer was added using a spatial intersection method in ArcGIS (Figure 3.6). The population densities measured correspondence to the three AusDiab data collection time points were used in Study Two, the residential density measured correspondence to AusDiab3 period was used in Study Three.

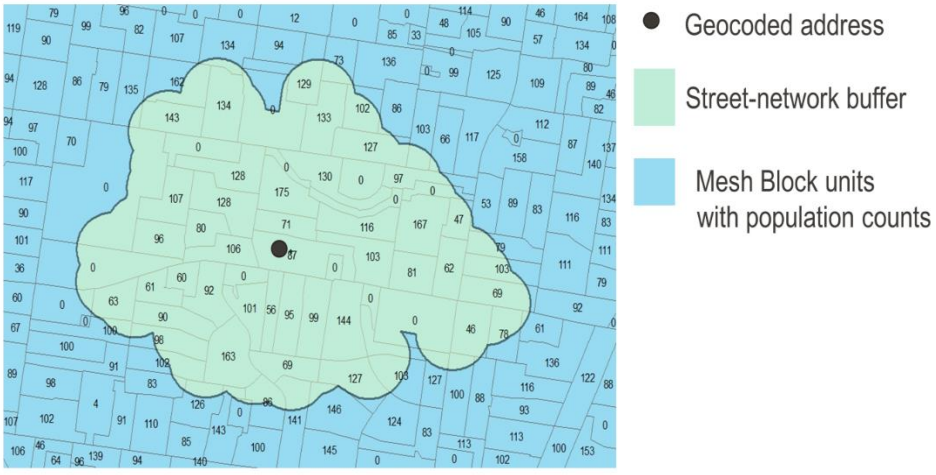


Figure 3.6: A Street-network Buffer Overlayed on Census Mesh Blocks

3.2.4.2 *Street connectivity*

Street connectivity was measured using intersection density, defined as the number of street intersections in the neighbourhood divided by its area (28). The road network data from PSMA Australia's Transport & Topography dataset (the 2012 release) was used to calculate intersections density. In GIS databases, streets are entered as a series of line segments that end at each intersection or connect to form a long street. The *Intersect* tool in ArcGIS was used to find locations of street intersections. Steps were taken to correctly identify the locations of street intersections (e.g., removing roundabouts circular lines using "transport hierarchy codes", manually checking locations of intersections within study areas and deleting duplicates). A density of 4-or-more way intersections was used in Study Three because it was observed that it can be a better measure of street connectivity than the density of 3-or-more way intersections (see Appendix AIII.3).

3.2.4.3 *Destination Density*

Destination density was defined as the total count of different types of destinations in the neighbourhood divided by its area. Destinations included were supermarkets, convenience stores, and public transport stops, which are considered as local destinations to which residents may travel daily/regularly (68). This destination-based measure was developed in Australia to assess land use diversity at the national scale and found to be correlated with an entropy measure of land use mix (68). Axiom Business Points data and Supermarkets data from Pitney Bowes Ltd (the 2014 release, sourced in 2012–2013) were used to obtain locations of convenience stores and supermarkets. PSMA Australia's Transport and Topography data (the 2012 release) was used to obtain locations of railway stations for commuters. General Transit Feed Specification online repository data (http://transitfeeds.com, sourced in 2015) were used to obtain locations of bus and tram stops.

3.2.4.4 *Other Environmental Attributes*

In addition to the above mentioned built environment attributes, a number of other attributes were also calculated for AusDiab participants, during the candidature. These include park measures (count, area, and proximity), PedShed ratio (ratio of the area within

street-network buffer to the area within straight-line buffer), street-network distance from participant's residence to the city centre, and Walk Score® (a web-based measure of walkability). However, these were not used in the empirical studies of this Thesis. In addition, 'Remoteness Area Index' was also obtained from the Census data. This area-level measure was used for performing stratified analyses according to the level of remoteness in Study Two. Methods used to measure these additional variables are described in Appendix III (AIII.4).

3.3 Analytical Sample and Variables Used

3.3.1 Analytical sample

The analytical sample used in this Thesis was defined as the AusDiab study participants who provided 12-year follow-up biomedical data and did not change their residence during the study period (stayers). There were 3,968 participants who provided data at all the three data collections and 646 participants who provided data at AusDiab1 and AusDiab3 only (4,614 with 12-year follow-up biomedical data). Of these, 2,369 were stayers, 2,164 were movers, and 81 had no address or addresses that could not be geocoded. Among the stayers, 15 participants who reported being pregnant at any data collection point were excluded from the analyses. The final sample retained for analyses in Study Two was 2,354. For Study Three, participants with chronic health conditions (n=331) were further excluded, since the study investigated the mediating role of physical activity, for which health conditions may have had stronger influences (rather than physical activity affecting cardio-metabolic health). The final analytical sample size for Study Three was 2,023. A flow chart describing the analytical sample is shown in Figure 3.7.

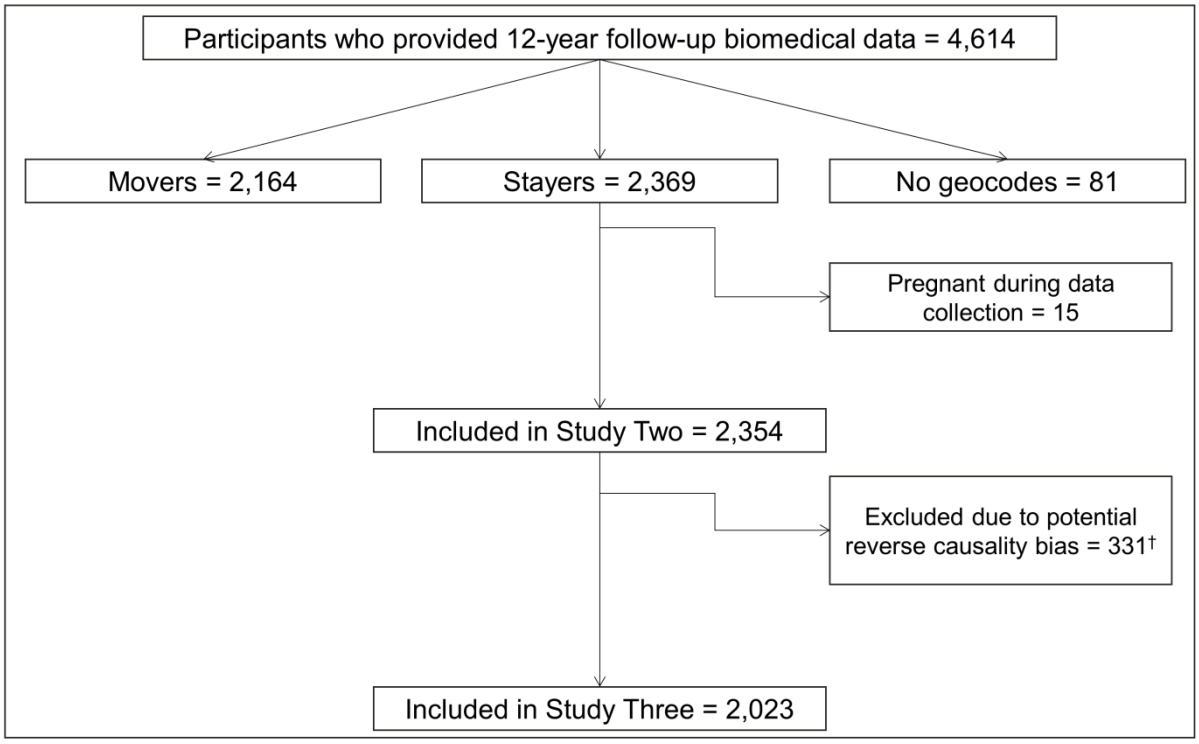


Figure 3.7: Flowchart of Analytical Samples

Note: † 151had heart disease; 209 had difficulties in walking; 11 were older than 78 years (numbers are not mutually exclusive)

3.3.2 Outcomes

In Chapter 2, it was identified that the lack of longitudinal studies investigating a broader range of cardio-metabolic risk markers is a research gap in this field. To address this gap, eight cardio-metabolic risk markers were examined in the empirical studies of this Thesis. These included waist circumference (WC), body weight (weight), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), 2-hour postload plasma glucose (2-hr PG), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). The methods used to measure these markers in the AusDiab study are described in Table 3.3. The outcomes of the two empirical studies are changes in these risk markers over 12 years. The methods used to calculate changes in risk markers, using values measured at three points, are described in Section 3.4.

Table 3.3: Measurement of Cardio-metabolic Risk Markers

Cardio-metabolic risk marker	**Measurement method**
Waist circumference (WC)	WC was measured using a measuring tape. Two measures were taken at halfway between the lower border of the ribs and the iliac crest on a horizontal plane. If the two measures varied by >2 cm, a third measure was taken; the mean of the two closest measurements was used.
Body weight	Weight was measured to the nearest 0.1 kg using a mechanical beam balance in 1999–2000 and digital weighing scales in 2004–05 and 2011–12.
Systolic blood pressure (SBP) and diastolic blood pressure (DBP)	Blood pressure was measured using automated blood pressure monitors (Dinamap® Pro-series Monitor) except for a manual sphygmomanometer used in Victoria in 1999–2000. Three sequential measurements were taken, with a 30-second interval between them. The mean of the two closest readings was used.
Fasting plasma glucose (FPG) and 2-hour postload plasma glucose (2-hr PG)	FPG was measured using the blood sample collected after an overnight fast. 2-hr PG was measured using the blood sample collected 2 hours after an oral glucose tolerance test (OGTT), which was performed to all participants except for those on diabetes medication. Plasma glucose levels were determined using automated analysers (Olympus AU600 in 1999–2000, Roche Modular in 2004–05, Siemens Advia 2400 in 2011-12)
High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG)	HDL-C and TG were measured using the blood sample collected after an overnight fast. Serum levels were determined using automated analysers (Olympus AU600 in 1999–2000, Roche Modular in 2004–05, Siemens Advia 2400 in 2011–12)

3.3.3 Exposures

3.3.3.1 *Population densification*

The systematic review identified that a majority of studies examined the cardio-metabolic health impacts of built environment attributes, which are measured at one point in time (often at baseline). Also, there has been limited research examining the cardio-metabolic health impacts of a specific built environment attribute. To address these gaps, the exposure variable investigated in Study Two was population densification, which was defined as the change in population density during the study period. Population density measures calculated at the three time points concordant with the AusDiab study's data collections were used to calculate the change in population density. The statistical method used to calculate the population densification variable is described in Section 3.4.

3.3.3.2 *Walkability index*

The systematic review found strong evidence for potential long-term protective effects of walkability against cardio-metabolic risk. However, the role of physical activity in these relationships was less clear. To address this gap, the exposure variable investigated in Study Three was a neighbourhood walkability index, which consisted of residential density, intersection density, and destination density. The walkability index was calculated by standardizing (z-score) the summed standardized scores of the three individual variables. As described above, these individual variables were calculated using geospatial data that were sourced around the time of AusDiab3.

3.3.4 Potential mediator

To assess the mediating role of physical activity, the total time spent in moderate-to-vigorous physical activity (including walking) was used. At each AusDiab data collection, participants were asked to report the time they spent in a range of physical activities during the previous week, using the Active Australia Survey (AAS) instrument (69). The specific items used to measure physical activity are presented in Appendix III (AIII.5). The total time (minutes per week) was calculated as the sum of the time spent in walking (for recreation and transport), moderate-intensity physical activity, plus double the time spent in vigorous-intensity physical activity (69). The AAS instrument has been shown to have acceptable levels of reliability and validity for the measure of weekly total physical

activity duration among adults (70, 71).

3.3.5 Potential confounders

The AusDiab study participants reported gender, age, education, marital status, employment status, household income, household children status (having a child or children in the household), medication use, and tobacco smoking. Their energy intake and alcohol intake were assessed using a food frequency questionnaire. These variables were considered as potential confounders, further details are provided in the corresponding chapters.

In addition, the Index of Relative Socioeconomic Disadvantage (IRSD), which is used to characterise area-level socioeconomic status in Australia, was used as a potential area-level confounder. The IRSD is a composite score defined for administrative areas, derived by ABS, using measures such as income, education, employment, household structure, and car ownership (72). Higher IRSD scores indicate lower levels of disadvantage. Statistical Local Area (SLA) of participants' residence, for which only IRSD scores were consistently available at the three corresponding Censuses, was used as the administrative area unit to obtain those scores.

3.4 Statistical Analysis

Study Two examined the impacts of changes in population density on changes in cardio-metabolic risk markers. Study Three investigated the mediating role of physical activity in the relationship between walkability and changes in cardio-metabolic risk markers. To carry out regression analyses in both studies, multilevel linear growth models were used. To assess mediation in Study Three, the joint-significance test was used. Details and rationale for the choice of these methods are described in the following subsections. To interpret regression results, statistical significance was set at $P<0.05$ and the corresponding 95% confidence intervals were presented; and $P<0.10$ was also considered as marginal significance (i.e., weaker evidence).

3.4.1 Multilevel linear growth models

The data used in the empirical studies of this Thesis has a three-level structure: repeated observations are nested within study participants who are nested within study areas (Figure 3.8). Failure to account for spatial clustering and temporal dependence in the regression modelling can increase the probability of committing Type I Error (i.e., likely to result in false 'significant' findings) (73). Use of the multilevel linear growth model is one way to appropriately analyse such multi-level data structure (73).

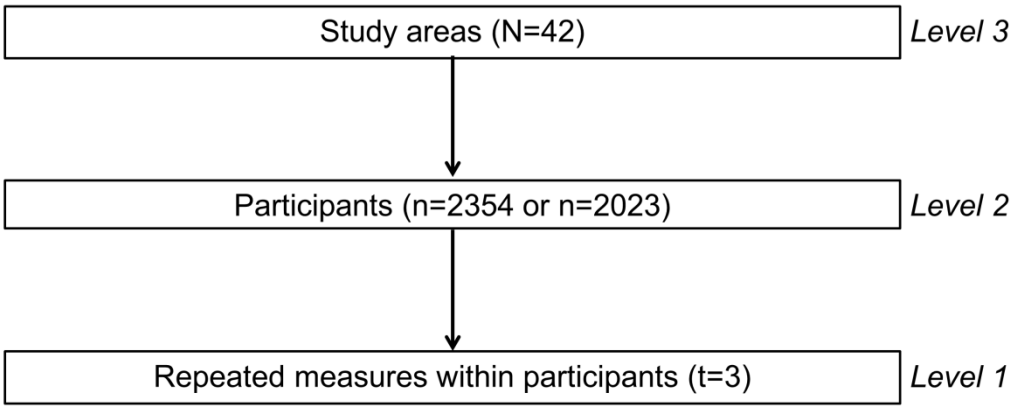


Figure 3.8: Three-level Structure of the Data used in Empirical Studies

In this multi-level data structure, the cardio-metabolic risk marker was assigned at Level 1 (at most, three repeated measures for each participant). The participant-specific exposure variable (in each study) was assigned at Level 2 (explained below). Participant-specific 'Time-Constant Confounders' (TCC), i.e. factors that do not change with time (e.g., gender), were assigned at Level 2. 'Time-Varying Confounders' (TVC) that are changing with time (e.g., income) were assigned at Level 1. Any area-level confounders that do not change with time can be assigned at Level 3 (in the current data, there were none). The multilevel linear growth model was developed as*:*

- Level 1 (time-level) model ⇒

$$y_{tij} = b_{0ij} + b_{1i}t + b_2 TVC_{ti} + e_{tij}$$

- Level 2 (participant-level) models ⇒

$$b_{0ij} = \beta_{00j} + \beta_{01}\, exposure_i + \beta_{02}\, TCC_i + u_{0ij}$$

$$b_{1i} = \beta_1 + \beta_{11}\, exposure_i + \beta_{11}\, TCC_i + u_{1i}$$

- Level 3 (area-level) model ⇒

$$\beta_{00j} = \gamma_{000} + v_{00j}$$

Here, y_{tij} is the value of the risk marker measured at time point t for study particpant i who resides in study area j. The random intercept b_{0ij} is the mean of y_{tij} across the time points for a particpant i who resides in a study area j. b_{0ij} is allowed to vary between particpants at Level 2 around β_{00j} (mean of y_{tij} across the time points for all particpants in a study area j). β_{00j} is allowed to vary between areas at Level 3 around the overall mean γ_{000}. The within-particpant change in the risk marker was operationalised by entering the *time metric* (i.e., measurement year, t=0, 5, or 12 in the study) at Level 1 and allowing its coefficient (slope of time) to vary at Level 2 (74). The random slope of the time metric (b_{1i}) represents the linear change in the risk marker for one unit incease in time, for particpant i (i.e., annual change in the risk marker) (74). The time-specifc residual is e_{ti}, and the particpant-specific random errors are u_{0ij} and u_{1i}, and the area-specific random error is v_{00j}.

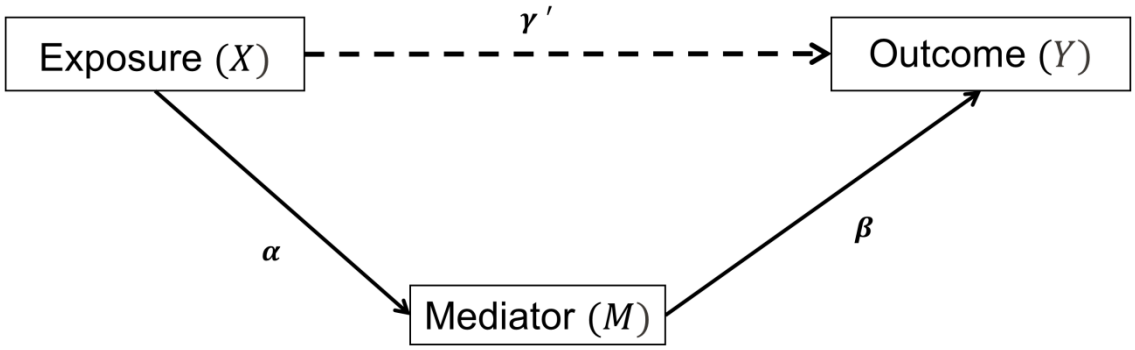
By incorporating the Level 3 and Level 2 equations in the Level 1 equation, a single equation model was obtained. The maximum likelihood estimation method was used to estimate the regression coefficients(73). The estimated value of the regression coefficient β_{11} and its confidence interval were used to report the relationship between the exposure variable and the annual change in the cardio-metabolic risk marker.

Also, an unconditional linear growth model (without conditioning on any covariates) was fitted for population density with corresponding Census years as time metrics (t=1 for 2001, t=6 for 2006, t=11 for 2011). The participant-specific random slope of the time metric in that model was used as the annual population densification in the corresponding participant's neighbourhood.

3.4.2 Mediation analysis

Figure 3.8 depicts an indirect effect of an exposure on the outcome through a mediator. Corresponding regression equations are also presented. To assess the mediating role of

physical activity in the relationship between walkability and changes in cardio-metabolic risk markers in Study Three, the joint-significance test was employed (75).



$$M = \beta_{0(\alpha)} + \alpha\, X\ + \epsilon$$

$$Y = \beta_{0(\beta)} + \gamma'\, X + \beta\, M + \epsilon$$

Figure 3.9: Diagrams and Regression Equations for Mediation Analysis

This test requires the following two conditions to hold to claim a significant mediating effect (75):

I. A statistically significant effect of the exposure on the mediator (i.e., α is significant)
II. A statistically significant exposure-adjusted effect of the mediator on the outcome (i.e., β is significant)

Several alternative statistical methods exist to assess mediating effects (75). MacKinnon et al. compared 14 such methods through a Monte Carlo study (simulation) and reported that the best balance of low Type I Error rate and the statistical power to detect a true mediating effect was found in the joint-significance test (75). Thus, it was decided to use this method in Study Three.

CHAPTER 4: NEIGHBOURHOOD POPULATION DENSIFICATION AND CARDIO-METABOLIC RISK

4.1 Urban Densification and 12-Year Changes in Cardiovascular Risk Markers (published peer-reviewed paper)

This chapter presents Study Two, which examined the potential impacts of changes in a specific built environment attribute on changes in cardio-metabolic risk markers among Australian adults. More specifically, as depicted in Figure 4.1, this study examined the impacts of population density increases in urban areas (referred to as urban densification) on the 12-year changes in multiple cardio-metabolic risk markers.

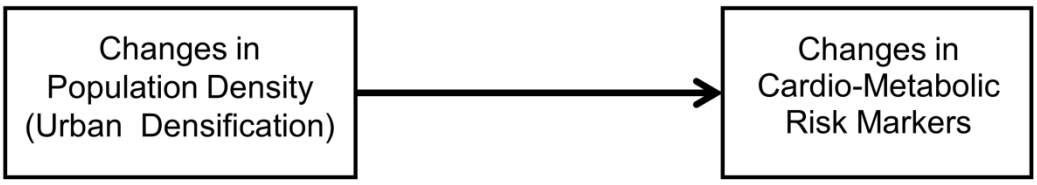


Figure 4.1: Conceptual Model for Study Two (Updated from Figure 2.1)

This manuscript has been published in the *Journal of the American Heart Association*. The nature and extent of contributions of authors are shown in Appendix I. To match with the scope of the journal, cardio-metabolic risk markers were referred to as cardiovascular risk markers in this manuscript.

Citation:

Chandrabose M, Owen N, Giles-Corti B, Turrell G, Carver A, Sugiyama T. Urban Densification and 12-Year Changes in Cardiovascular Risk Markers. J Am Heart Assoc. 2019;8(15): e013199. doi:10.1161/JAHA.119.013199

ORIGINAL RESEARCH

Urban Densification and 12-Year Changes in Cardiovascular Risk Markers

Manoj Chandrabose, MPhil; Neville Owen, PhD; Billie Giles-Corti, PhD; Gavin Turrell, PhD; Alison Carver, PhD; Takemi Sugiyama, PhD

***Background*—**Population densities of many cities are increasing rapidly, with the potential for impacts on cardiovascular health. This longitudinal study examined the potential impact of population-density increases in urban areas (urban densification) on cardiovascular risk markers among Australian adults.

***Methods and Results*—**Data were from the Australian Diabetes, Obesity and Lifestyle Study, in which adult participants' cardiovascular risk markers were collected in 3 waves (in 1999–2000, 2004–2005, and 2011–2012). We included 2354 participants with a mean age of 51 years at baseline who did not change their residence during the study period. Outcomes were 12-year changes in waist circumference, weight, systolic and diastolic blood pressure, fasting and 2-hour postload plasma glucose, high-density lipoprotein cholesterol, and triglycerides. The exposure was neighborhood population densification, defined as 12-year change in population density within a 1-km radius buffer around the participant's home. Multilevel linear growth models, adjusting for potential confounders, were used to examine the relationships. Each 1% annual increase in population density was related with smaller increases in waist circumference (b=−0.043 cm/y; 95% CI, −0.065 to −0.021 [P<0.001]), weight (b=−0.019 kg/y; 95% CI, −0.039 to 0.001 [P=0.07]), and high-density lipoprotein cholesterol (b=−0.035 mg/dL per year; 95% CI, −0.067 to −0.002 [P=0.04]), and greater increases in diastolic blood pressure (b=0.032 mm Hg/y; 95% CI, −0.004 to 0.069 [P=0.08]).

***Conclusions*—**Our findings suggest that, at least in the context of Australia, urban densification may be protective against obesity risk but may have adverse effects on blood lipids and blood pressure. Further research is needed to understand the mechanisms through which urban densification influences cardiovascular health. **(*J Am Heart Assoc*. 2019;8:e013199. DOI: 10.1161/JAHA.119.013199.)**

Key Words: environmental epidemiology • heart disease • population health • type 2 diabetes mellitus • urbanization

The global burden of cardiometabolic disease is increasing.[1,2] In 2015, an estimated 423 million people worldwide experienced cardiovascular disease[1] and 415 million had diabetes mellitus.[3] A basic premise of preventive medicine is that a large number of people at low risk will contribute more to the burden of disease than a small number who are at high risk.[4] Thus, along with clinical approaches for those who are at high risk, community-wide strategies are also necessary to lower the risk for the total population. In this context, investigating the role of contextual factors has been identified as one of the key directions for the future of cardiovascular epidemiology.[5,6]

Population density—the number of people living per unit area can be a fundamental health-related attribute of neighborhood environments.[7] A number of studies, mostly conducted in Western countries, have reported associations of population density with health behaviors and outcomes. For example, an Australian study reported that higher-density

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Accompanying text S1, Tables S1 through S3, and Figure S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013199

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Clinical Perspective

What Is New?

- In the global context of urbanization, where cities are growing in size and urban population densities are increasing, this longitudinal study identified the potential impacts of urban densification on Australian adults' cardiovascular risk.

What Are the Clinical Implications?

- Characteristics of urban environments may have complex impacts on the susceptibility to cardiovascular disease: population-density increase may be protective against obesity but may elevate risk of hypertension.
- Clinicians can take into account such emerging risk exposures, which are broader and ubiquitous determinants of cardiovascular health.

urban neighborhoods with better access to local stores and services can facilitate active modes of travel, such as walking,[8] which are associated with lower cardiovascular risk.[9] Car use is predominant in sprawling lower-density outer suburbs in Australia.[10] Living in outer suburban neighborhoods has also been shown to increase obesity risk in Australia.[11] Cross-sectional studies have shown associations of higher population density with lower risk of obesity and type 2 diabetes mellitus in North America[12,13] and with lower risk of hypertension in France.[14] A longitudinal study has found that higher density at baseline was associated with reduced incidence of cardiovascular events in women in the United States.[15] A systematic review of longitudinal studies found evidence for potential long-term protective effects of higher walkability, typically consisting of measures related to population density, land use, and street layout, against cardiometabolic disease risk.[16]

Little is known, however, about how changes in population density in neighborhoods may influence residents' cardiovascular health. Examining the potential impacts of population-density increases (densification) is timely in the global context of widespread, rapid urbanization.[17] Urban dwellers increased from 30% of the world population in 1950 to 54% in 2015, and this is expected to reach 60% in 2030.[18] Although urban densification is a global trend, only a few studies have examined the cardiovascular health impacts of population density change over time.[16] For example, an increase in population density, measured at a large scale (metropolitan statistical area), was found to be inversely associated with an increase in body mass index over 30 years in the United States.[19] Also, increases in a composite environmental index (consisting of population density, land use, and density of destinations) have been found to be associated with smaller increases in body mass index and waist circumference over 9 years in the United States.[20] To better understand such impacts, research is needed on whether population-density increases at a local scale can influence indices of cardiovascular risk.

We examined longitudinal relationships of urban population densification with changes in Australian adults' cardiovascular risk markers over 12 years.

Methods

Data Source and Study Participants

We used data from the AusDiab (Australian Diabetes, Obesity and Lifestyle Study), an Australian national cohort study examining the risk factors, prevalence, and incidence of diabetes mellitus and cardiovascular disease. Survey and biomedical data were collected in 3 waves: 1999–2000 (AusDiab1), 2004–2005 (AusDiab2), and 2011–2012 (AusDiab3). Detailed descriptions of study design, recruitment procedures, and measurement methods have been published.[21] Briefly, AusDiab1 used a 2-stage stratified cluster sampling method in which study participants were randomly selected from 42 urban sites chosen from each of six Australian states and Northern territory. Each site consisted of contiguous Census Collection Districts (CCDs). A CCD was the smallest geographic area unit for the collection of Census data at the time of AusDiab1, averaging ≈225 dwellings.[22] In total, 11 247 adults aged 25 years and older with no physical or intellectual disabilities and who resided at their addresses for 6 months or longer before the survey were recruited. The overall response rate for biomedical examinations at baseline was 55.3%.[21]

From the baseline cohort, 6400 (59.3%) and 4614 (44.6%) participants completed surveys and biomedical examination for AusDiab2 and AusDiab3, respectively. There were 3968 participants who provided data in all 3 waves, and 646 who attended both AusDiab1 and AusDiab3. We excluded participants whose addresses were not accurately geocoded (n=81), those who were pregnant (n=39) during the data collection, and those who changed their residence during the study period (n=2140). "Movers" were excluded because their relocation date was not recorded, which prevented us from accurately examining neighborhood effects. The final sample retained for analyses was 2354 (2119 provided data at 3 waves, and 235 at the first and third waves only). The International Diabetes Institute and the Alfred Hospital ethics committee (no. 39/11) approved the study, and written informed consent was obtained from all participants.

Outcome Measures

The outcomes of this study were the changes in cardiovascular risk markers over 12 years. These included waist circumference (WC), body weight (weight), systolic blood

pressure (BP), diastolic BP (DBP), fasting plasma glucose (fpg), 2-hour postload plasma glucose (2-hour PG), high-density lipoprotein cholesterol (HDL-C), and triglycerides. They were measured at local data collection centers at each time point. Details of the instruments used to measure these markers have been described elsewhere.[21] Methods to calculate the annual change for each outcome are described below in the Statistical Analysis section.

Exposure Measure

The exposure variable was population densification, which was defined as the change in population density during the study period. Population density is defined as the number of individuals living in a geographical unit divided by its area.[23] In this study, we calculated population density for each participant for the area within a 1-km radius buffer around his/her residence using Census data corresponding to each data collection time point. We used a straight-line buffer rather than a street-network buffer to have the same geographical area across all the waves. The population count data in the smallest geographical units covering all Australia (CCDs in 2001 for AusDiab1; mesh blocks in 2006 and 2011 for AusDiab2 and AusDiab3) were obtained from the relevant Census unit. Population counts for an individual buffer were calculated by summing the population counts of the Census areas included in the buffer. If the buffer intersected a Census unit (CCD or mesh block), that unit's population count corresponding to the percentage of the area within the buffer was added. Population density was expressed as persons per hectare (pph). Methods to calculate population densification are explained below in Statistical Analysis. We expressed the population densification as a relative measure in percentage [(density change/baseline density)×100] so that a unit increase had the same magnitude relative to the baseline density. We also used an absolute measure of densification, pph per year, as a secondary unit. ArcGIS (version 10.6) was used for calculating population density.

Covariates

Potential covariates included time, which corresponded to repeated measures of outcome variables; time-constant covariates: sex, education, height (only for weight), family history of diabetes mellitus, baseline population density; and time-varying covariates assessed at each wave: age, marital status, employment status, household income, household children status (having a child or children in the household), medication use for hypertension, medication use for high cholesterol, energy intake, tobacco smoking, alcohol intake, and area-level socioeconomic status. For area-level socioeconomic status, we used the Index of Relative Socio-Economic Disadvantage (IRSD),[24] which is a composite variable defined for geographic areas, derived using measures such as income, education, employment, household structure, and car ownership, with higher scores indicating lower levels of disadvantage. The IRSD was defined at the Statistical Local Area of participants' residence and obtained for each AusDiab wave from the corresponding Censuses. Because of potential overadjustment, we did not adjust for physical activity variables (eg, walking) that may mediate the relationships examined.[25]

Statistical Analysis

To calculate participants' annual change in cardiovascular risk markers, we fitted an unconditional linear growth model, in which we used fixed continuous time metrics: t=0 for AusDiab1 (baseline); t=5 for AusDiab2 (5-year follow-up); and t=12 for AusDiab3 (12-year follow-up). The participant-specific random slopes of this growth model were used as the annual changes in the risk marker.[26] We also fitted an unconditional linear growth model of population density with corresponding Census years as time metrics (t=1 for 2001, t=6 for 2006, and t=11 for 2011). The participant-specific random intercepts (at t=0) and the random slopes of this growth model were used as the baseline population density at year 2000 and annual population densification, respectively. This method enabled us to obtain robust estimates of annual changes in outcomes and exposure by utilizing the information available at all 3 waves and corresponding Census years.[27]

Multilevel linear growth models[28] were used to examine associations of population densification with changes in cardiovascular risk markers. In the multilevel models, the model intercept was allowed to vary between participants and between study sites, to account for intraindividual correlations attributable to repeated measures and area-level clustering attributable to stratified cluster sampling. Three sets of models were fitted for each outcome. Model 1 adjusted for baseline population density. Model 2 further adjusted for individual-level sociodemographic variables and IRSD. Model 3 further adjusted for health- and behavior-related factors including family history of diabetes mellitus (only for fpg and 2-hour PG), medication use for hypertension (only for systolic BP and DBP), medication use for high cholesterol (only for HDL-C and triglycerides), energy intake, tobacco smoking, and alcohol intake. Further details of multilevel growth models are explained in accompanying text S1 and Figure S1.

We conducted sensitivity analyses focusing on residents of metropolitan areas. The AusDiab study included sites from both metropolitan and regional cities of Australia. Since population densification can be considered more prominent in

metropolitan areas, we ran model 3 after excluding participants who resided in regional cities (n=1080), as defined by Australian Statistical Geography Standard Remoteness Area Classification.[29]

Multilevel modeling of repeated measures over time assumes a missing at random mechanism implying that models will result in unbiased estimates if all variables related to attrition are included in the model.[28] Statistical analyses were performed in STATA (version 15.0; StataCorp). Statistical significance was set at $P<0.05$.

Results

Table 1 shows the baseline characteristics of study participants. The mean follow-up duration was 11.9 years (range: 11.0 to 12.4 years). The comparison of baseline characteristics of those included in the current study (stayers), excluded from the study (movers), and who dropped out of the AusDiab study is shown in Table S1. Compared with the stayers, the movers consisted of slightly more women and more workers, and the dropouts were more likely to be older, had lower educational qualifications, had lower income levels, did not work, did not live with a partner or children, and had poorer health profiles at baseline.

Table 2 shows the mean overall change (from AusDiab1 to AusDiab3) and the mean annual change (estimated from the unconditional growth models) of each cardiovascular risk marker. On average, participants increased their WC, weight, BP, and glucose levels but improved their lipid profiles (increased HDL-C and decreased triglycerides) over the 12-year period.

The mean baseline population density was 13.0 pph (SD=7.4, median=12.1, range: 0.5 to 52 pph). The mean annual relative population densification estimated from the unconditional growth model was 0.8% per year (SD=1.3, median=0.7, range: −4.1 to 7.8% per year). The mean annual absolute population densification was 0.09 pph/y (SD=0.13, median=0.08, range: −0.20 to 1.23 pph/y). Approximately one fifth of participants (19%) lived in areas where population density decreased during the study period. It should be noted that the relative and absolute densification are distinct measures of population-density changes. Although they were correlated ($r=0.65$, $P<0.01$), higher relative densification tended to occur in areas with lower baseline density, while higher absolute densification was more likely to take place in areas with higher baseline density (Figure S1 and S2).

Table 3 shows the results of multilevel linear growth models, examining linear associations of annual relative densification with annual changes in cardiovascular risk markers. After adjusting for baseline population density (model 1), a 1% annual increase in population density was associated with smaller increases in WC (b=−0.047 cm/y; 95% CI, −0.067 to −0.026 [$P<0.001$]), weight (b=−0.025 kg/y; 95% CI, −0.044 to −0.006 [$P=0.01$]), and HDL-C (b=−0.038 mg/dL per year; 95% CI, −0.067 to

Table 1. Selected Characteristics of Study Participants (N=2354) at Baseline in AusDiab (1999–2012)

Baseline Characteristics	Mean±SD or Percentage
Age, y	51.1±10.8
Women	53.6
Education	
High school or less	34.5
Technical or less	43.3
Bachelor's degree or higher	22.2
Employment status	
Working	70.7
Not working	28.8
Other	0.4
Weekly household income	
<$600	31.0
$600 to 1500	46.2
>$1500	22.8
Marital status, couple	85.2
Children in household	45.2
Cardiovascular risk markers	
WC, cm	89.7±13.4
Weight, kg	76.2±15.6
SBP, mm Hg	128.3±17.5
DBP, mm Hg	70.8±11.5
FPG, mg/dL	99.5±18.9
2-h PG, mg/dL	109.2±37.4
HDL-C, mg/dL	55.4±14.4
Triglycerides, mg/dL	131.5±87.9
Health-related behaviors	
Energy intake, kJ/d	8131±3277
Tobacco smoking, current or past smoker	38
Alcohol intake, g/d	14.3±17.9
Family history of diabetes mellitus	19.6
Medication use	
For hypertension	12.1
For high cholesterol	7.7
Index of relative socioeconomic disadvantage	1023±62

2-h PG indicates 2-hour postload plasma glucose; AusDiab, Australian Diabetes Obesity and Lifestyle Study; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.

Table 2. Overall Changes and Annual Change Rates in Cardiovascular Risk Markers in AusDiab (1999–2012)

Cardiovascular Risk Marker	Mean±SD Overall Changes*	Mean±SD Annual Change Rates†
WC, cm	5.20±7.53	0.433±0.237
Weight, kg	2.02±7.08	0.163±0.322
SBP, mm Hg	2.77±18.18	0.283±0.167
DBP, mm Hg	1.81±12.69	0.169±0.462
FPG, mg/dL	0.37±20.32	0.042±0.855
2-h PG, mg/dL	2.73±36.01	0.307±0.988
HDL-C, mg/dL	3.39±10.63	0.292±0.278
Triglycerides, mg/dL	−12.66±75.53	−1.076±2.377

2-h PG indicates 2-hour postload plasma glucose; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.
*Measure at AusDiab3 (Australian Diabetes Obesity and Lifestyle Study)—measure at AusDiab1.
†Estimated from the unconditional growth model.

−0.009 [*P*=0.009]). Statistical adjustment for sociodemographic (model 2) and behavior- and health-related factors (model 3) did not markedly alter the regression coefficients and statistical significance for WC but slightly attenuated the associations for weight (*P*=0.07 in model 3) and HDL-C (*P*=0.04 in model 3). Additionally, in model 3, a 1% annual increase in population density was marginally associated with a greater increase in DBP (b=0.032 mm Hg/y; 95% CI, −0.004 to 0.069 [*P*=0.08]).

The regression results obtained using the absolute measure of densification (pph/y) are shown in Table S2. We observed consistent but more statistically significant inverse associations for WC, weight, and HDL-C, and an additional significant association for 2-hour PG. In model 3, each 1-pph annual increase in population density was associated with smaller increases in WC (b=−0.38 cm/y; 95% CI, −0.60 to −0.15 [*P*<0.001]), weight (b=−0.19 kg/y; 95% CI, −0.40 to 0.02 [*P*=0.08]), 2-hour PG (b=−1.96 mg/dL per year; 95% CI, −3.16 to −0.77 [*P*=0.001]), and HDL-C (b=−0.59 mg/dL per year; 95% CI, −0.93 to −0.25 [*P*=0.001]).

The results of the sensitivity analyses, focusing only on participants who resided in metropolitan areas (n=1274), are shown in Table S3. Similar to those reported in Table 3 (model 3), relative densification was associated with changes in WC and HDL-C (borderline significant). However, relative densification in metropolitan areas was also associated with greater increases in DBP and systolic BP (borderline significant). The absolute population densification in metropolitan areas was associated with changes in HDL-C (same as model 3 in Table S2) but was not associated with WC and 2-hour PG changes.

Discussion

In this cohort of Australian adults, participants' cardiovascular risk increased on average during the 12-year study period, with the exception of a slight improvement in lipid profiles. In Australia, the mean annual increase in WC is about 0.45 cm among adults,[30] which is consistent with the estimated annual increase in our sample. We found that changes in some cardiovascular risk markers varied by population densification. Increases in urban population density were

Table 3. Associations of Annual Relative Population Densification With Changes in Cardiovascular Risk Markers in AusDiab (1999–2012)

Cardiovascular Risk Markers	Unstandardized Regression Coefficients (95% CI)		
	Model 1	Model 2	Model 3
WC, cm	−0.047 (−0.067 to −0.026)*	−0.048 (−0.069 to −0.026)*	−0.043 (−0.065 to −0.021)*
Weight, kg	−0.025 (−0.044 to −0.006)†	−0.018 (−0.038 to 0.002)‡	−0.019 (−0.039 to 0.001)‡
SBP, mm Hg	0.020 (−0.029 to 0.070)	0.021 (−0.031 to 0.073)	0.018 (−0.037 to 0.072)
DBP, mm Hg	0.025 (−0.01 to 0.059)	0.028 (−0.007 to 0.063)	0.032 (−0.004 to 0.069)‡
FPG, mg/dL	−0.018 (−0.073 to 0.038)	−0.019 (−0.071 to 0.033)	−0.008 (−0.062 to 0.045)
2-h PG, mg/dL	−0.077 (−0.182 to 0.027)	−0.084 (−0.193 to 0.026)	−0.076 (−0.191 to 0.039)
HDL-C, mg/dL	−0.038 (−0.067 to −0.009)§	−0.036 (−0.067 to −0.006)†	−0.035 (−0.067 to −0.002)†
Triglycerides, mg/dL	0.007 (−0.197 to 0.211)	0.058 (−0.155 to 0.271)	0.034 (−0.190 to 0.258)

Regression coefficients correspond to 1% annual increase in population density relative to the baseline population density. Model 1: adjusted for baseline population density and corrected for clustering. Model 2: further adjusted for age, sex, education, employment status, household income, marital status, household children status, height (only for weight), and Index of Relative Socio-Economic Disadvantage. Model 3: further adjusted for energy intake, tobacco smoking, alcohol intake, family history of diabetes mellitus (for fasting plasma glucose [FPG] and 2-hour plasma glucose [2-hour PG] only), hypertensive medication use (for systolic blood pressure [SBP] and diastolic blood pressure [DBP] only), and cholesterol medication use (for high-density lipoprotein cholesterol [HDL-C] and triglycerides only). AusDiab indicates Australian Diabetes Obesity and Lifestyle Study; WC, waist circumference.
*$P<0.001$; †$P<0.05$; ‡$P<0.10$; §$P<0.01$.

beneficially associated with changes in obesity-related measures, after adjusting for multiple potential confounders including energy intake. The estimated effect size was greater for WC change than for body weight change, suggesting that increasing urban densification may have a protective effect against abdominal obesity, which is a strong marker of cardiometabolic disease risk.[31]

We found that the study areas varied by 12% in their annual population densification (range: −4% to 8%). Since the regression coefficient for WC change was −0.043 cm for 1% annual density increase, those living in areas with −4% densification would have an additional 0.52 cm (=0.043×12) greater increase in WC per year, relative to those living in areas with 8% densification. At the population level, such differences in WC increases accumulated over years would be substantial. The potential protective effects of increasing population density against obesity may be greater in Australian capital cities such as Sydney and Melbourne, where large populations reside in neighborhoods with increasing density, which was around 4% annually in the past 5 years.[32]

Our findings on the associations between population densification and obesity measures are consistent with 2 previous longitudinal studies conducted in the United States.[19,20] Although these studies did not use a direct measure of population-density change measured at a local scale, our findings along with these studies suggest that increasing population density may reduce the risk of obesity in localities with lower population density. Increasing population density can increase access to more walkable destinations in the neighborhood.[17] Residents in such neighborhoods may, for example, engage in more active travel and rely less on cars for transport, which can have a protective effect against chronic diseases over time.[33,34] Further research is needed to examine the potential role of active travel and car use in the impact of densification on obesity.

We did not find associations of relative or absolute densification with BP changes, except for a borderline adverse association between relative densification and DBP. However, in the sensitivity analysis undertaken on metropolitan participants, we found higher relative densification to be associated with greater increases in the BP measures. This finding was unexpected. There is strong longitudinal evidence for the relationships between higher walkability (a composite measure including population density) and lower risk of hypertension.[16,35] Thus, it was anticipated that increasing population density would have beneficial effects on BP. It is not possible to explain our present findings (no associations for the whole sample, but adverse associations for the metropolitan sample). Potential explanations may include nonlinear relationships between densification and BP changes, or detrimental impacts by unmeasured factors related to urban densification (eg, increased air and noise pollution from traffic, reduced exposure to green space, and enhanced access to unhealthy food and alcohol). If the beneficial impact of densification on obesity-related measures is attributable to physical activity, there may be other pathways for BP that overshadow the benefits from being active. Given that cities across the globe are increasing their density, further studies are needed to examine multiple pathways and quantify each of their potential mediating effects to fully understand both the beneficial and detrimental impacts of urban densification. Future research can explore further how to avoid or mitigate harmful cardiovascular health effects of densification.

No associations were found between relative densification and blood glucose measures. However, absolute densification was beneficially associated with 2-hour PG in all models, but not with fasting plasma glucose (Table S2). Overall, it can be argued that increasing population density has some modest benefits for blood glucose, potentially attributable to physical activity increases. On the contrary, we found that both relative and absolute densification measures had adverse effects on HDL-C, but they were not associated with triglycerides (Table 3 and Table S2). It is unclear as to why densification had differential impacts on blood glucose and lipid measures. It is also unclear why the 2 densification measures produced distinct results for postload blood glucose (significant results found for absolute densification). It is not possible to disentangle the effects of densification on blood glucose and lipids, but these findings suggest that densification may be both beneficial and detrimental to cardiometabolic health. Studies on potential mediating factors may provide insights into the way population densification influences residents' blood glucose and lipid measures.

Study Strengths and Limitations

Our study has several strengths. We used robust objective measures for both the outcomes and exposure at 3 time points with a 12-year follow-up duration. The study sites ranged from metropolitan to regional cities, which provided a wide range of variation in population density changes. We used multilevel growth models to analyze the relationships between densification and within-participant changes in cardiovascular risk markers, sequentially adjusting for potential time-constant and time-varying confounders. A limitation is that while our findings may be generalizable to localities with lower population density, they may not be applicable to very high-density cities. Future research needs to investigate the impacts of density increase in higher-density localities as further densification may produce adverse cardiovascular health effects. The attrition rate was relatively high because of the longer follow-up period (55%). Our modeling approach assumes a "missing at random" mechanism, where it has

been shown that up to 60% attrition was less likely to produce biased estimates under this missingness mechanism.[36] However, if attrition was caused by a "missing not at random" mechanism, the effect sizes may have been underestimated.[36] Further selection of participants as a result of their relocation status could also lead to selection bias, if the relocation status is patterned by participants' cardiovascular risk status.[36] Since the aim of our study was to examine the total effects (through direct and potential pathways) of population densification on cardiovascular risk changes over time, we did not examine the mediating mechanisms or effect modifications. Understanding mechanisms (contextual variables such as access to public transport or individual behaviors such as physical activity) through which urban densification influences cardiovascular health is an important future research topic. Research is also needed to examine whether the potential cardiovascular impacts of densification varies by population subgroups (eg, sex, socioeconomic status, and ethnicity) and among different levels of area-level socioeconomic status, for whom disparities in cardiovascular health has been observed.[37]

Conclusions

Urban densification is a global phenomenon, which also applies to Australian cities. The expansion of growth boundaries to allow low-density residential development in urban peripheries is a commonly used strategy to accommodate urban population increases. Our findings suggest that increasing population in existing neighborhoods (while not expanding the growth boundary) may be protective against obesity. However, we also found potential detrimental effects of densification on BP and on blood lipids. Further studies in different localities with higher baseline density such as Asian and European cities and investigating behavioral and other factors that may mediate the effects are warranted to better understand the potential cardiovascular impacts of urban densification. Research is also needed to test whether there are population-density thresholds above which further population increases may elevate cardiovascular disease risk.

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Disclosures

None.

References

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Arnlov J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Barnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castaneda-Orjuela CA, Castillo-Rivas J, Catala-Lopez F, Choi JY, Christensen H, Cirillo M, Cooper L Jr, Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70:1–25.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87:4–14.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017;128:40–50.
4. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 2001;30:427–432.
5. Sallis JF, Floyd MF, Rodriguez DA, Saelens BE. Role of built environments in physical activity, obesity, and cardiovascular disease. *Circulation*. 2012;125:729–737.
6. Vasan RS, Benjamin EJ. The future of cardiovascular epidemiology. *Circulation*. 2016;133:2626–2633.
7. Stevenson M, Thompson J, de Sa TH, Ewing R, Mohan D, McClure R, Roberts I, Tiwari G, Giles-Corti B, Sun XD, Wallace M, Woodcock J. Land use, transport, and population health: estimating the health benefits of compact cities. *Lancet*. 2016;388:2925–2935.
8. Bentley R, Blakely T, Kavanagh A, Aitken Z, King T, McElwee P, Giles-Corti B, Turrell G. A longitudinal study examining changes in street connectivity, land use, and density of dwellings and walking for transport in Brisbane, Australia. *Environ Health Perspect*. 2018;126:057003.
9. Panter J, Mytton O, Sharp S, Brage S, Cummins S, Laverty AA, Wijndaele K, Ogilvie D. Using alternatives to the car and risk of all-cause, cardiovascular and cancer mortality. *Heart*. 2018;104:1749–1755.
10. Sugiyama T, Merom D, van der Ploeg HP, Corpuz G, Bauman A, Owen N. Prolonged sitting in cars: prevalence, socio-demographic variations, and trends. *Prev Med*. 2012;55:315–318.
11. Sugiyama T, Niyonsenga T, Howard NJ, Coffee NT, Paquet C, Taylor AW, Daniel M. Residential proximity to urban centres, local-area walkability and change in waist circumference among Australian adults. *Prev Med*. 2016;93:39–45.
12. Glazier RH, Creatore MI, Weyman JT, Fazli G, Matheson FI, Gozdyra P, Moineddin R, Kaufman-Shriqui V, Booth GL. Density, destinations or both? A

comparison of measures of walkability in relation to transportation behaviors, obesity and diabetes in Toronto, Canada. *PLoS ONE*. 2014;9:e85295.

13. Rundle A, Diez Roux AV, Free LM, Miller D, Neckerman KM, Weiss CC. The urban built environment and obesity in New York City: a multilevel analysis. *Am J Health Promot*. 2007;21:326–334.
14. Chaix B, Ducimetiere P, Lang T, Haas B, Montaye M, Ruidavets JB, Arveiler D, Amouyel P, Ferrieres J, Bingham A, Chauvin P. Residential environment and blood pressure in the PRIME Study: is the association mediated by body mass index and waist circumference? *J Hypertens*. 2008;26:1078–1084.
15. Griffin BA, Eibner C, Bird CE, Jewell A, Margolis K, Shih R, Ellen Slaughter M, Whitsel EA, Allison M, Escarce JJ. The relationship between urban sprawl and coronary heart disease in women. *Health Place*. 2013;20:51–61.
16. Chandrabose M, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, Giles-Corti B, Sugiyama T. Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. *Obes Rev*. 2019;20:41–54.
17. Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, Foster S, Lowe M, Sallis JF, Stevenson M, Owen N. City planning and population health: a global challenge. *Lancet*. 2016;388:2912–2924.
18. UN. *World Urbanization Prospects: The 2018 Revision*. New York, NY: United Nations Department of Economic and Social Affairs; 2018.
19. Zhao Z, Kaestner R. Effects of urban sprawl on obesity. *J Health Econ*. 2010;29:779–787.
20. Hirsch JA, Moore KA, Barrientos-Gutierrez T, Brines SJ, Zagorski MA, Rodriguez DA, Diez Roux AV. Built environment change and change in BMI and waist circumference: multi-ethnic Study of Atherosclerosis. *Obesity*. 2014;22:2450–2457.
21. Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw JE, De Courten M, Jolley D, McCarty DJ, Committee AS. The Australian diabetes, obesity and lifestyle study (AusDiab)—methods and response rates. *Diabetes Res Clin Pract*. 2002;57:119–129.
22. ABS. Statistical geography—Australian standard geographical classification (ASGC), digital boundaries, 2006 (cat. no. 1259.0.30.002). Canberra: Australian Bureau of Statistics; 2006.
23. Cervero R, Kockelman K. Travel demand and the 3Ds: density, diversity, and design. *Transport Res D-Tr E*. 1997;2:199–219.
24. ABS. Census of population and housing: socio-economic indexes for areas (SEIFA), Australia (cat. no. 2033.0.55.001). Canberra: Australian Bureau of Statistics; 2011.
25. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009;20:488–495.
26. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. *Annu Rev Psychol*. 2011;62:583–619.
27. Curran PJ, Obeidat K, Losardo D. Twelve frequently asked questions about growth curve modeling. *J Cogn Dev*. 2010;11:121–136.
28. Hox JJ. *Multilevel analysis: techniques and applications*. New York, NY: Routledge; 2010.
29. ABS. Australian statistical geography standard (ASGS): volume 5–remoteness structure (cat. no. 1270.0.55.005). Canberra: Australian Bureau of Statistics; 2011.
30. ABS. Profiles of health, Australia, 2011–13 (cat. no. 4338.0). Canberra: Australian Bureau of Statistics; 2012.
31. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Obesity*. 2007;15:1061–1067.
32. ABS. Regional population growth, Australia (cat. no. 3218.0). 2018.
33. Sugiyama T, Wijndaele K, Koohsari MJ, Tanamas SK, Dunstan DW, Owen N. Adverse associations of car time with markers of cardio-metabolic risk. *Prev Med*. 2016;83:26–30.
34. Zwald ML, Fakhouri THI, Fryar CD, Whitfield G, Akinbami LJ. Trends in active transportation and associations with cardiovascular disease risk factors among U.S. adults, 2007–2016. *Prev Med*. 2018;116:150–156.
35. Chiu M, Rezai MR, Maclagan LC, Austin PC, Shah BR, Redelmeier DA, Tu JV. Moving to a highly walkable neighborhood and incidence of hypertension: a propensity-score matched cohort study. *Environ Health Perspect*. 2016;124:754–760.
36. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2003;19:751–760.
37. Mensah GA, Cooper RS, Siega-Riz AM, Cooper LA, Smith JD, Brown CH, Westfall JM, Ofili EO, Price LN, Arteaga S, Parker MCG, Nelson CR, Newsome BJ, Redmond N, Roper RA, Beech BM, Brooks JL, Furr-Holden D, Gebreab SY, Giles WH, James RS, Lewis TT, Mokdad AH, Moore KD, Ravenell JE, Richmond A, Schoenberg NE, Sims M, Singh GK, Sumner AE, Trevino RP, Watson KS, Aviles-Santa ML, Reis JP, Pratt CA, Engelgau MM, Goff DC, Perez-Stable EJ. Reducing cardiovascular disparities through community-engaged implementation research: a National Heart, Lung, and Blood Institute Workshop Report. *Circ Res*. 2018;122:213–230.

CHAPTER 5: NEIGHBOURHOOD WALKABILITY, PHYSICAL ACTIVITY, AND CARDIO-METABOLIC RISK

5.1 Neighbourhood Walkability and 12-year Changes in Cardio-metabolic Risk: The Mediating Role of Physical Activity (published peer-reviewed paper)

This chapter presents Study Three, which investigated the potential mediating role of physical activity in the relationship between walkability and changes in multiple cardio-metabolic risk markers among Australian adults. This manuscript has been published in the *International Journal of Behavioral Nutrition and Physical Activity (IJBNPA)*. The nature and extent of contributions of authors are shown in Appendix I.

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Neighborhood walkability and 12-year changes in cardio-metabolic risk: the mediating role of physical activity

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Abstract

Background: Living in walkable neighborhoods may provide long-term cardio-metabolic health benefits to residents. Little empirical research has examined the behavioral mechanisms in this relationship. In this longitudinal study, we examined the potential mediating role of physical activity (baseline and 12-year change) in the relationships of neighborhood walkability with 12-year changes in cardio-metabolic risk markers.

Methods: The Australian Diabetes, Obesity and Lifestyle study collected data from adults, initially aged 25+ years, in 1999–2000, 2004–05, and 2011–12. We used 12-year follow-up data from 2023 participants who did not change their address during the study period. Outcomes were 12-year changes in waist circumference, weight, systolic and diastolic blood pressure, fasting and 2-h postload plasma glucose, high-density lipoprotein cholesterol, and triglycerides. A walkability index was calculated, using dwelling density, intersection density, and destination density, within 1 km street-network buffers around participants' homes. Spatial data for calculating these measures were sourced around the second follow-up period. Physical activity was assessed by self-reported time spent in moderate-to-vigorous physical activity (including walking). Multilevel models, adjusting for potential confounders, were used to examine the total and indirect relationships. The joint-significance test was used to assess mediation.

Results: There was evidence for relationships of higher walkability with smaller increases in weight ($P = 0.020$), systolic blood pressure ($P < 0.001$), and high-density lipoprotein cholesterol ($P = 0.002$); and, for relationships of higher walkability with higher baseline physical activity ($P = 0.020$), which, in turn, related to smaller increases in waist circumference ($P = 0.006$), weight ($P = 0.020$), and a greater increase in high-density lipoprotein cholesterol ($P = 0.005$). There was no evidence for a relationship of a higher walkability with a change in physical activity during the study period ($P = 0.590$).

Conclusions: Our mediation analysis has shown that the protective effects of walkable neighborhoods against obesity risk may be in part attributable to higher baseline physical activity levels. However, there was no evidence of mediation by increases in physical activity during the study period. Further research is needed to understand other behavioral pathways between walkability and cardio-metabolic health, and to investigate any effects of changes in walkability.

Keywords: Built environment, Cardiovascular disease, Type 2 diabetes, Hypertension, Pathways, Population health

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Background

Due to the increasing global burden of cardio-metabolic diseases, such as type 2 diabetes (T2D) and cardiovascular disease, urgent preventive action has been advocated [1]. In addition to individual-level approaches to reducing risk factors, greater attention is now being given to community-level approaches that address the contextual factors where people live [2]. A growing body of research has examined the role of the built environment in cardio-metabolic disease prevention [3–6]. A recent review of longitudinal studies found that residents living in higher walkability neighborhoods (characterized by high residential density, mixed land use, and high street connectivity) are less likely to develop obesity, T2D, and hypertension over time, compared with those who live in lower walkability neighborhoods [3]. Environmental initiatives to reduce cardio-metabolic disease risk are promising as they are likely to have sustained effects at the community level [7].

It is important to identify behavioral pathways that may underlie the relationships between the built environment and cardio-metabolic disease [3–7]. This could inform the development of effective environmental and policy initiatives for targeting chronic disease prevention [7]. Physical activity is a strong candidate for mediating these relationships. Neighborhood environmental attributes including walkability are associated with residents' physical activity levels [8–11], and regular participation in physical activity reduces cardio-metabolic disease risk [12–14]. However, existing studies examining the mediating role of physical activity in the relationships between walkability and cardio-metabolic health have in most part focused on cross-sectional associations with obesity-related outcomes [15–17]. The findings of those studies suggest indirect associations between walkability and obesity-related outcomes through physical activity. In order to further advance our understanding, it is important to examine how physical activity, which may change over time, accounts for the long-term health benefits of neighborhood walkability [3]. Further, it is known that active lifestyles can be effective in improving other cardio-metabolic health profiles (blood pressure, blood glucose, and blood lipids), independent of their effects on obesity-related measures [18]. Thus, research needs to further examine the potential mediating effects of physical activity in the relationship of walkability with multiple markers of cardio-metabolic disease.

Three longitudinal studies have examined the mediating role of physical activity in relationships between walkability and cardio-metabolic health outcomes [19–21]. Two tested mediation by using the Barron and Kenny's approach [22], examining the attenuation in the relationship between walkability and cardio-metabolic health by comparing regression coefficients before and after adjusting for physical activity [20, 21]. This approach, however, is not in line with recent advances in methods of mediation analysis [23, 24]. Indeed, tests of mediation based on the Barron and Kenny's approach have been found to provide incorrect findings [25, 26]. Further, this approach relies on the total effect (direct and through all possible mediating pathways) of the exposure on the outcome being statistically significant in order to assess mediation (indirect) effects. However, it is now recognized that an indirect effect of the exposure on the outcome through mediators can exist even in the absence of a significant total effect (i.e., multiple opposite directional mediators exist and cancel each other out) [23, 24]. One recommended way to test mediating effects is to separately assess the effects of exposures on mediators and the exposure-adjusted effects of mediators on outcomes [23, 25]. An Australian study used this method to assess the mediating role of physical activity measured at a single time point in the relationship of walkability with 10-year changes in glycosylated hemoglobin (HbA1c, a marker of cardio-metabolic disease) and found a partial mediation effect [19]. However, the mediating role of physical activity change in the relationship of walkability with residents' cardio-metabolic health over time has not been examined.

The aims of our study were twofold: first, to examine the total effects of neighborhood walkability on 12-year changes of cardio-metabolic risk markers (estimating γ in Fig. 1a); second, to examine the indirect effects of neighborhood walkability on changes in the outcomes, mediated through physical activity at baseline and changes in physical activity (estimating α and β in Fig. 1b). We hypothesized that high walkability would be protective against increasing cardio-metabolic risk over time, and that those protective effects would be partly attributable to high baseline levels and subsequent increases in physical activity.

Methods

Data source

Data were from the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), which is an Australian national longitudinal cohort study [27]. The primary aim of AusDiab is to examine the prevalence and determinants of obesity, diabetes, and cardiovascular disease. AusDiab collected survey and biomedical data in three waves: baseline in 1999–2000 (AusDiab1), first follow-up in 2004–05 (AusDiab2), and second follow-up in 2011–12 (AusDiab3). Details about the AusDiab1 study design and recruitment procedures have been published elsewhere [27]. Briefly, a two-stage stratified cluster sampling design was used to select 42 study areas in the metropolitan and regional cities of six states and the Northern Territory. From each study area, a random sample of adults (aged 25 years and over, with no

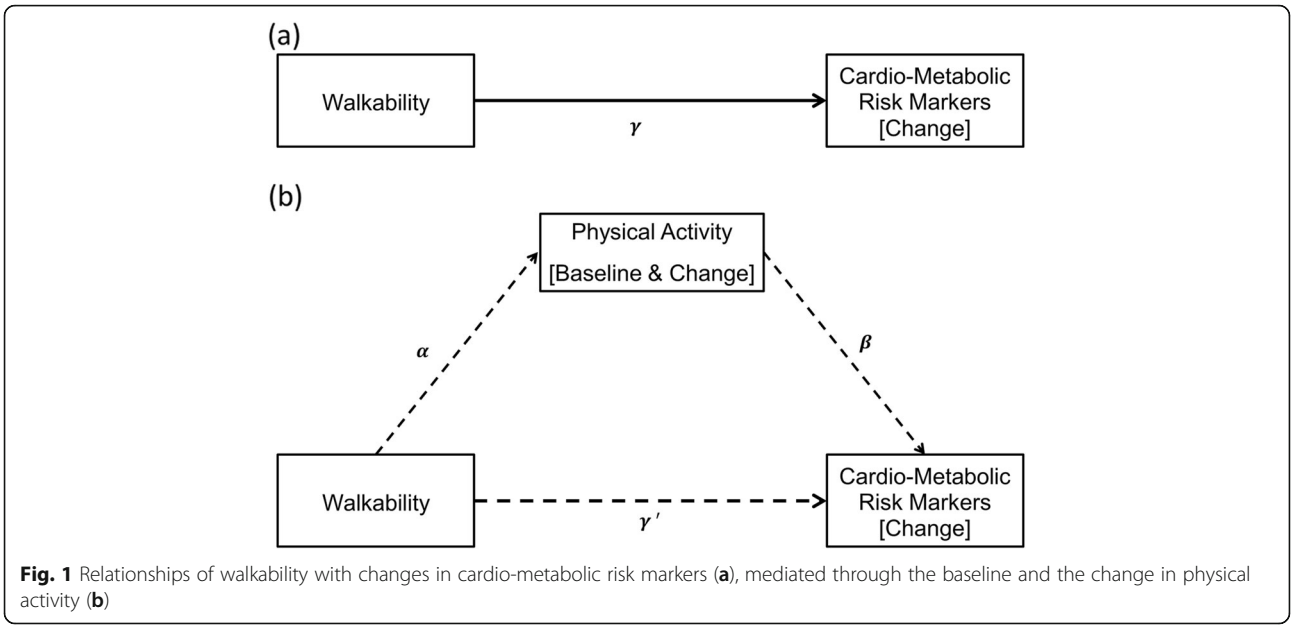

Fig. 1 Relationships of walkability with changes in cardio-metabolic risk markers (**a**), mediated through the baseline and the change in physical activity (**b**)

physical or intellectual disabilities, and residing at their addresses for 6 months or longer prior to the survey) was selected. A study area consisted of contiguous Census Collector District (CCD) geographical area units. A CCD was the smallest area unit for the collection of Census data at the time of AusDiab1, averaging approximately 225 dwellings [28]. In total, 11,247 participants provided both survey and biomedical data in AusDiab1 (response rate = 55.3%). From the baseline cohort, 6400 (retention rate = 59.3%) and 4614 (retention rate = 44.6%) participants provided both survey and biomedical data in AusDiab2 and AusDiab3, respectively. The International Diabetes Institute and the Alfred Hospital Ethics Committee approved the study (approval no. 39/11). All participants provided written informed consent to participate in the study.

Study participants

Our sample consisted of participants for whom data were available over 12 years. There were 3968 who provided data at all three observation points, and 646 who provided data for AusDiab1 and AusDiab3 only. Of these, we excluded those whose addresses were not accurately geocoded ($N = 81$) and who moved residence during the study period ($N = 2140$). The reason for excluding movers was that it is unknown for how long they were exposed to different neighborhoods between observation points since their relocation date was not recorded. Further, we excluded 15 participants who reported being pregnant during data collection; 151 who reported that they had coronary heart disease or stroke prior to or during the study period; 209 who reported difficulties in walking more than 500 m at any of three observation points; and 11 who were older than 78 years at baseline [29] (numbers are not mutually exclusive). The reason for excluding these subgroups was to reduce possible reverse causality bias, as their health status may have had stronger influences on their physical activity behaviors during the study period [30]. The final analytical sample size was 2023.

Outcome variables

The outcomes examined were annual changes in cardio-metabolic risk markers over 12 years: waist circumference (WC), body weight (weight), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), 2-h postload plasma glucose (2-h PG), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). These markers were measured at local data-collection centers at each time point. The details of the measurement methods and instruments used were described previously [27].

Exposure variables

The primary exposure variable of our study was a neighborhood walkability index. The walkability index typically consists of measures of residential density, street connectivity, and land use mix [31]. Given the difficulty of obtaining nationally consistent fine-scale land use data for calculating land use mix (entropy) measures in Australia, Mavoa et al. [32] developed an alternative measure using access to daily living destinations. Following their method, we created a walkability index using residential density, street connectivity, and daily living destinations. They were calculated for each participant within a 1 km street-network buffer (sausage-type, with

150 m radius from street centerline) around their residential location [33]. We chose a 1 km buffer to represent residential neighborhoods because this distance was shown to be a typical distance within which most neighborhood walking trips by adults take place [34]. In the current study, it was not possible to obtain retrospective spatial data, for calculating walkability, that corresponds to the baseline of the study (1999–2000). We, thus, sourced spatial data around the second follow-up period. The details of each of the walkability components are given below. ArcGIS v.10.6 (ESRI, Redlands) was used for geographic information system (GIS) data processing and spatial analysis.

Residential density

Residential density was defined as the number of dwellings within the buffer divided by its area. The dwelling count data in the mesh blocks (smallest census geographical units) were obtained from the Australian Bureau of Statistics 2011 Census [35] to calculate an individual buffer based dwelling density measure [36].

Street connectivity

We used intersection density as the measure of street connectivity. Intersection density was defined as the number of 4-or-more way intersections within the buffer divided by its area, which has previously been shown to be associated with walking in the context of Australia [37]. Road network data from PSMA Australia's 2012 Transport & Topography dataset were used to calculate this measure.

Daily living destinations

Access to daily living destinations was measured as the density (total count divided by buffer area) of different types of neighborhood destinations to which residents may travel daily/regularly: supermarkets, convenience stores, and public transport stops. This destination-based measure was developed in Australia to assess land use diversity at the national scale, and found to be correlated with an entropy measure of land use mix and associated with walking for transport [32]. Axiom Business Points data and Supermarkets data from Pitney Bowes Ltd. (sourced in 2013) were used to obtain locations of convenience stores and supermarkets. PSMA Australia's 2012 Transport data were used to obtain locations of railway stations for commuters. General Transit Feed Specification online repository data (http://transitfeeds.com, sourced in 2015) were used to obtain locations of tram stops. Bus stops were not used in this study because their inclusion inflates this measure (about 90% of participants had at least one bus stop and over 25% of participants had 25+ bus stops within 1 km buffer).

Walkability index

A walkability index was calculated by standardizing (z-score) the summed standardized measures of residential density, intersections density, and daily living destinations density.

Mediating variables

Participant's self-reported time spent in physical activity was used to obtain the two potential mediator variables. At each wave of the AusDiab study, participants were asked to report the time they spent in a range of physical activities during the previous week using the Active Australia Survey (AAS) [38, 39]. The items used were shown in Additional file 1: Material S1. Total time (mins per week) was calculated as the sum of the time spent in walking (for recreation and transport), moderate-intensity physical activity, plus double the time spent in vigorous-intensity physical activity [39]. The AAS instrument has been shown to have acceptable levels of reliability and validity for the measure of weekly total physical activity duration among adults [40, 41]. To avoid measurement error due to over-reporting, we truncated the weekly total physical activity duration at 1680 min (28 h) per week following the AAS procedure [39]. Total time at AusDiab1 was used as the baseline measure. To estimate the annual change in physical activity, we calculated the 12-year change in physical activity geometrically, as shown in Additional file 1: Material S2. This method allowed us to incorporate all three time points in assessing the change in physical activity. This is superior to a simpler method of subtracting the baseline value from the 12-year follow-up value, which disregards the 5-year follow-up value and assumes a constant change throughout the study period.

Potential confounders

We included the following variables (assessed at baseline) as potential confounders: gender, age, education, marital status, employment status, household income, household children status (having a child or children in the household), and height (for weight only). Since a change in participants' socio-demographic status over time may influence their long-term physical activity and cardio-metabolic health profiles, we also included changes (from baseline to wave 3) in marital status, employment status, household income, and household children status as potential confounders of the relevant longitudinal models. For instance, change in employment status was classified as: kept working, stopped working, started working, or not working. Further, hypertension medication use (for SBP and DBP only), medication/insulin treatment for diabetes or family history of diabetes (for FPG and 2-h PG only), and cholesterol medication use (for HDL-C and TG only) were

included as potential confounders in the relevant models. These variables are defined as binary variables (yes: participant was on medication in at least one of the three observation points; no: participant was not on medication at any observation point). For area-level socioeconomic status, we used the Index of Relative Socioeconomic Disadvantage (IRSD), which is a census-based composite variable consisting of measures such as income, education, employment, household structure, and car ownership [42]. The 2011 IRSD scores corresponding to the Australian Standard Geographical Classification's Statistical Local Area (SLA) units were used. For the study areas that sat across multiple SLAs, the mean IRSD value was employed (12 study areas sat across two SLAs and one study area sat across three SLAs).

Statistical analyses

Calculating changes in cardio-metabolic risk markers

We used multilevel unconditional linear growth models to estimate each participant's annual change in cardio-metabolic risk markers by utilizing measures at three observation points [43]. Briefly, for each risk marker, repeated measures (of individuals who were nested within study sites) were modeled with the time at which the corresponding measure was obtained as a predictor. We used continuous time metrics: t = 0 for AusDiab1 (baseline); t = 5 for AusDiab2 (5-year follow-up); and t = 12 for AusDiab3 (12-year follow-up). These multilevel (three-level) growth models included random intercepts at the participant and the study area level and random slopes for time metrics at the participant level. Inclusion of random intercepts for participants allowed those observations from the same participants (repeated measures) to be correlated, and inclusion of random intercepts for study areas allowed those participants living in the same areas (participants recruited from pre-selected CCDs) to be correlated. Participant-specific random intercept and random slope of time metric (corresponding to participant's linear trajectory line) estimated the starting point and the annual change of the risk marker, respectively [see Additional file 1: Material S2]. An unstructured covariance matrix was specified between participant-specific random intercepts and random slopes to allow them to correlate. The point estimate of the regression coefficient of time represents the annual change for the average participant.

Examining the total effects

To examine the total effect of the walkability index on changes in cardio-metabolic risk markers (corresponding to γ in Fig. 1a), the above described multilevel linear growth models were extended by adding the walkability index and other potential confounders as participant-level and area-level predictors (see Additional file 1: Material S3 for further details) [44].

Testing mediation

To test mediation, we estimated regression coefficients α and β in Fig. 1b. For α, we used a two-level generalized linear mixed model with a Gamma distribution and log link function to examine the relationship of the walkability index with baseline physical activity (right-skewed); and a two-level linear mixed model with a Normal distribution and identity link function to examine the relationship of the walkability index with changes in physical activity (Normally distributed). In both models, random intercepts were included at the study area level to account for area-level clustering. The model for baseline physical activity was adjusted for the baseline socio-demographic variables only; while the model for change in physical activity was adjusted for both baseline and change in socio-demographic variables, and baseline physical activity. For β, the above described multilevel linear growth models to estimate the total effects were extended by further adding the baseline and changes in physical activity along with the walkability index and potential confounders. To assess the statistical significance of the mediating effect, we used the joint-significance test [26], in which simultaneous significance of the regression coefficients α and β provides evidence for mediating effects.

Missing data and loss to follow-up

In multi-level linear growth models, for each risk marker outcome variable, all participants with at least a baseline measurement for the corresponding marker were included in the analyses. Multilevel modeling of repeated measures over time assumes missing at random (MAR) mechanism for missing data, implying that missingness can be ignored if all variables related to attrition are included in the model [44].

Statistical analyses were performed in STATA (v.15.0) and R (v.3.5.0).

Results

Table 1 shows the characteristics of the study sample. The mean follow-up duration was 11.9 years (range: 11.0 to 12.4 years). The comparison of baseline characteristics of those included in the current study (stayers), excluded (movers), and who withdrew from the AusDiab study is shown in Additional file 1: Table S1. Compared with those who provided 12-years follow-up data, movers were more likely to be younger and not living with a partner, while drop-outs were more likely to be older, less educated, had lower income levels, not working, not living with a partner or children, had poorer health profiles and having lower physical activity levels at baseline.

Table 1 Baseline characteristics of study participants, AusDiab study, 1999–2000, ($N = 2023$)

Baseline characteristics	Means (SD) or Percentages
Age, years	49.8 (10.2)
Gender, % Women	54.5
Education	
% High school or less	33.1
% Technical or vocation	43.1
% Bachelor's degree or more	23.8
Employment status	
% Working	74.3
% Not working	25.1
% Others	0.6
Weekly household income	
% Less than $600	27.4
% $600–1500	48.0
% > $1500	24.7
Marital status, % couple	86.1
Children in household, % yes	48.3
Cardio-metabolic risk markers	
WC (cm)	88.7 (13.1)
Weight (kg)	75.5 (15.4)
SBP (mmHg)	127.0 (16.7)
DBP (mmHg)	70.4 (11.3)
FPG (mg/dL)	98.7 (17.6)
2-h PG (mg/dL)	107.3 (35.6)
HDL-C (mg/dL)	55.9 (14.6)
TG (mg/dL)	127.8 (87.4)
Total physical activity (hours/week)	5.0 (6.1)
Walking (hours/week)	2.1 (2.7)
Moderate-intensity physical activity (hours/week)	1.0 (2.7)
Vigorous-intensity physical activity (hours/week)	0.9 (2.0)
Medication use (reported at least at one wave)	
For hypertension, % yes	32.1
For type 2 diabetes (including insulin), % yes	4.8
For high cholesterol, % yes	23.5
Family history of diabetes (pooled across waves), % yes	29.0
Index of Relative Socioeconomic Disadvantage (2011 Census)	1021.4 (58.6)

Abbreviations: *WC* Waist Circumference, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FPG* Fasting Plasma Glucose, *2-h PG* 2-h Postload Plasma Glucose, *HDL-C* High-Density Lipoprotein Cholesterol, *TG* Triglycerides

Table 2 shows descriptive statistics for the walkability index and its components, and Pearson's correlation coefficients between each pair of them. Correlation coefficients between walkability components ranged from 0.4 to 0.6.

Table 3 shows the mean change from AusDiab1 to AusDiab3 and the mean annual change (estimated from the unconditional growth models) of each cardio-metabolic risk marker. Overall, on average, participants increased their WC, weight, blood pressure, and glucose levels, but improved their lipid profiles over the 12-year period. The mean (SD) weekly total physical activity duration at baseline was 5.0 (6.1) hours/week and its mean change over the 12-year study period was 1.2 (9.3) hours/week (i.e., increase).

Table 4 shows the results of regression models examining the total effects of walkability index on annual changes in cardio-metabolic risk markers (γ regression coefficients). After adjusting for potential confounders, there was evidence for relationships of higher walkability index with smaller annual increases in weight ($P = 0.028$), SBP ($P < 0.001$), and HDL-C ($P = 0.002$); and there was also some weaker evidence for relationships of higher walkability index with smaller annual increases in WC ($P = 0.092$) and FPG ($P = 0.053$).

With regard to the associations of walkability index with the baseline and the annual change in physical activity (α coefficients), after adjusting for potential confounders, there was evidence for the relationship of higher walkability index with higher baseline physical activity (exp(α) [95% CI] = 1.09 [1.01, 1.16], $P = 0.020$); but not with the annual change in physical activity (α [95% CI] = 0.01 [− 0.03, 0.05] hours/week, $P = 0.590$).

Table 5 shows the results of regression models examining the effects of the baseline and the annual change in physical activity on annual changes in cardio-metabolic risk markers (β regression coefficients). After adjusting for walkability index and other potential confounders, there was evidence for relationships of higher baseline physical activity with smaller increases in WC ($P = 0.006$), weight ($P = 0.020$), and a greater increase in HDL-C ($P = 0.005$). In the corresponding regression models, there was evidence for relationships of an increase in physical activity related with smaller increases in WC ($P < 0.001$), weight ($P = 0.005$), DBP ($P = 0.050$), FPG ($P = 0.019$), TG ($P = 0.004$), and a greater increase in HDL-C ($P < 0.001$).

Discussion

This study examined the total effects of neighborhood walkability on cardio-metabolic risk changes over 12 years, and whether physical activity mediated these relationships. Below, we first discuss our findings on the total effects, mediation by physical activity (baseline and change), followed by limitations and strengths.

Total effects

For the total effect of walkability on cardio-metabolic risk markers, we found evidence that higher walkability

Table 2 Descriptive statistics for walkability and its components within participants' 1 km street-network residential buffers, AusDiab study, 1999–2012, (*N* = 2023)

Walkability components	Mean (SD)	Min	Q1	Median	Q3	Max	Correlation Matrix			
							Res. density	Int.density	Des.density	Walkability
Res. density [a]	7.1 (3.6)	0.1	4.5	6.6	9.4	26.2	1.0	0.6*	0.4*	0.8*
Int. density [b]	4.0 (4.5)	0.0	0.8	2.3	5.2	20.7		1.0	0.4*	0.8*
Des. density [c]	1.5 (1.5)	0.0	0.0	1.2	2.3	8.1			1.0	0.7*
Walkability	0.0 (1.0)	−1.6	−0.7	− 0.2	0.6	5.1				1.0

Abbreviations: *Res* Residential, *Int* Intersections, *Des* Destinations;
*$P < 0.001$
[a]Number of dwellings/hectare within 1 km of each residence
[b]Number of 4-way intersections/km^2 within 1 km of each residence
[c]Number of daily living destinations/km^2 within 1 km of each residence

index was related to smaller increases in weight and related to smaller increases in WC (weaker evidence). These findings suggest that living in high walkable areas may be protective against the development of obesity. We observed that one standard deviation (SD) higher walkability index was related to smaller annual weight gain by 0.03 kg (Table 4). Considering that the mean annual weight gain for this sample was 0.18 kg (Table 3), the total effect of one SD higher walkability on residents' weight gain was around 17%, which can be interpreted as being a substantial effect at the population level [45]. A recent systematic review of longitudinal studies found strong evidence for a protective effect of higher walkability against the development of obesity [3]. Our study thus contributes to this growing evidence base, which suggests that initiatives to improve neighborhood walkability could make an important contribution to reducing the burden of obesity [46].

For blood pressure markers, we found that a higher walkability index was related to smaller increases in SBP, but not DBP. A recent study conducted in the UK also reported similar findings [47]. Further, the finding on the effect of higher walkability on SBP change was also consistent with two studies conducted in the USA [48, 49]. For blood glucose markers, we found that higher walkability index was related to smaller increases in FPG, but not with 2-h PG. Other studies have also produced mixed findings for relationships of walkability with changes in T2D risk markers [19, 48, 50]. The systematic review of longitudinal studies found strong evidence for potential protective effects of higher walkability against the development of hypertension and T2D [3]. Our current findings partly support the beneficial relationship of walkability with blood pressure and blood glucose found in existing studies. For blood lipid markers, we found that higher walkability index was related to a smaller increase in HDL-C, but not with TG. Notably, the relationship between walkability and HDL-C was in the unexpected direction (living in a high walkable neighborhood leading to poorer blood lipid profiles). This finding is, to some extent, consistent with a previous longitudinal study conducted in the USA that found a greater increase in TG for those who moved to higher walkability neighborhoods from lower walkability neighborhoods [50]. A recent systematic review of mostly cross-sectional studies also found less favorable blood lipid levels among urban residents as compared with rural residents [51]. These inconsistent or

Table 3 Mean changes cardiometabolic risk markers, AusDiab study, 1999–2012, (*N* = 2023)

Cardiometabolic Risk markers	No of participants included in models	Mean (95% CI) change from AusDiab1 to 3	Mean[a] (95% CI) annual change
WC (cm)	2023	5.35 (5.02, 5.67)	0.45 (0.42, 0.47)
Weight (kg)	2019	2.25 (1.95, 2.54)	0.18 (0.16, 0.21)
SBP (mmHg)	2019	3.00 (2.25, 3.74)	0.30 (0.24, 0.36)
DBP (mmHg)	2019	2.20 (1.66, 2.74)	0.20 (0.16, 0.25)
FPG (mg/dL)	2023	−0.08 (− 0.93, 0.77)	0.01 (− 0.06, 0.08)
2-h PG (mg/dL)	1997	1.97 (0.39, 3.56)	0.15 (0.02, 0.29)
HDL-C (mg/dL)	2023	3.58 (3.12, 4.05)	0.31 (0.27, 0.35)
TG (mg/dL)	2023	−10.24 (− 13.54, −6.94)	−0.87 (− 1.15, − 0.6)

Abbreviations: *WC* Waist Circumference, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FPG* Fasting Plasma Glucose, *2-h PG* 2-h Postload Plasma Glucose, *HDL-C* High-Density Lipoprotein Cholesterol, *TG* Triglycerides
[a]Estimated from the unconditional growth model

Table 4 Total effects of walkability index on annual changes in cardio-metabolic risk markers, AusDiab study, 1999–2012, ($N = 2023$)

Cardio-metabolic risk marker	γ- regression coefficients (95%CI)	*P*-value
WC (cm)	−0.02 (− 0.05, 0.00)	0.092
Weight (kg)	−0.03 (− 0.05, 0.00)	**0.028**
SBP (mmHg)	−0.15 (− 0.21, − 0.08)	**< 0.001**
DBP (mmHg)	0.01 (− 0.03, 0.05)	0.552
FPG (mg/dL)	−0.06 (− 0.13, 0.00)	0.053
2-h PG (mg/dL)	0.01 (− 0.11, 0.14)	0.826
HDL-C (mg/dL)	−0.06 (− 0.10, − 0.02)	**0.002**
TG (mg/dL)	0.04 (− 0.18, 0.26)	0.702

Abbreviations: *WC* Waist Circumference, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FPG* Fasting Plasma Glucose, *2-h PG* 2-h Postload Plasma Glucose, *HDL-C* High-Density Lipoprotein Cholesterol, *TG* Triglycerides
Models adjusted for baseline age, gender, education, baseline work status, baseline household income, baseline marital status, baseline household children status, changes in socio-demographic factors (work status, household income, marital status, and household children status), height (only for weight), hypertension medication use (for SBP and DBP only), treatment for diabetes and family history of diabetes (for FPG and 2-h PG only), cholesterol medication use (for HDL-C and TG only), and Index of Relative Socio-economic Disadvantage. Regression coefficients correspond to 1 SD increment in walkability index. *P*-value < 0.05 in boldface

unexpected findings may be due to other potentially relevant exposures not measured in this study, such as easier access to unhealthy food outlets [52], which may have some detrimental effects on blood pressure, glucose, and lipids. Future research might consider examining the spatial co-location of walkability and other environmental exposures to investigate their independent and joint relationships with cardio-metabolic disease risk.

Mediation by baseline physical activity

Based on the joint-significance test, we found evidence suggesting that baseline physical activity mediates the relationship between walkability and changes in obesity-related measures (i.e., higher walkability index was related with higher baseline physical activity, which predicted smaller annual increases in WC and weight). This finding is consistent with previous cross-sectional studies on mediation by physical activity in the relationship between walkability and obesity [15–17], using mediation analysis methods similar to those used in this study. However, our study extends the previous findings by showing the mediating role of physical activity in the long-term protective effect of higher walkability against obesity. The mediation analysis also found that higher baseline physical activity, which was related to higher walkability, had a beneficial impact on cholesterol. This is contradictory to the observed total effect, where higher walkability led to adverse cholesterol changes over time. It is possible that higher walkability itself has positive effects on blood lipids through facilitating physical activity. But, as discussed above, walkable neighborhoods may also provide easy access to unhealthy food outlets [52]. The detrimental effects of greater energy intake may have outweighed the benefits provided by greater physical activity. This warrants further

Table 5 Relationships of the baseline and the annual change in physical activity with annual changes in cardio-metabolic risk markers, adjusted for walkability index, AusDiab study, 1999–2012 ($N = 2023$)

Cardio-metabolic risk markers	β– regression coefficients			
	Baseline physical activity (hours/week)		Change in physical activity (hours/week)	
	β (95%CI)	*P*-value	β (95%CI)	*P*-value
WC (cm)	−0.008 (− 0.014, − 0.002)	**0.006**	−0.096 (− 0.139, − 0.053)	**< 0.001**
Weight (kg)	−0.006 (− 0.011, − 0.001)	**0.020**	−0.056 (− 0.094, − 0.017)	**0.005**
SBP (mmHg)	−0.001 (− 0.013, 0.012)	0.926	0.023 (− 0.070, 0.116)	0.624
DBP (mmHg)	−0.004 (− 0.011, 0.004)	0.372	−0.058 (− 0.116, 0.000)	0.050
FPG (mg/dL)	−0.005 (− 0.016, 0.006)	0.382	−0.099 (− 0.181, − 0.016)	**0.019**
2-h PG (mg/dL)	−0.011 (− 0.038, 0.015)	0.397	−0.155 (− 0.354, 0.044)	0.126
HDL-C (mg/dL)	0.012 (0.004, 0.020)	**0.005**	0.158 (0.095, 0.221)	**< 0.001**
TG (mg/dL)	−0.028 (− 0.074, 0.018)	0.236	− 0.516 (− 0.863, − 0.169)	**0.004**

Abbreviations: *WC* Waist Circumference, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FPG* Fasting Plasma Glucose, *2-h PG* 2-h Postload Plasma Glucose, *HDL-C* High-Density Lipoprotein Cholesterol, *TG* Triglycerides. Models adjusted for walkability index, baseline age, gender, education, baseline work status, baseline household income, baseline marital status, baseline household children status, changes in lifestyle factors (work status, household income, marital status, and household children status), height (only for weight), hypertension medication use (for SBP and DBP only), treatment for diabetes and family history of diabetes (for FPG and 2-h PG only), cholesterol medication use (for HDL-C and TG only), and Index of Relative Socio-economic Disadvantage. *P*-value < 0.05 in boldface

investigation. Research incorporating multiple relevant health behaviors is needed to understand the seemingly contradictory findings.

Notably, no evidence was found for relationships of physical activity measured at baseline with changes in blood pressure, blood glucose, and triglycerides. A possible explanation may be that in the context that physical activity changes over a longer follow-up period, the baseline physical activity may fail to predict the long-term beneficial health gains [53–55].

Mediation by changes in physical activity

We also examined whether changes in physical activity levels over time may be a factor mediating the relationships between neighborhood walkability and changes in cardio-metabolic risk. Although physical activity changes were related to changes in most of the risk markers examined in the study, walkability (measure at a single time point) was not related to physical activity changes. Thus, according to the joint-significance test, physical activity changes may not be considered as a mechanism through which neighborhood walkability influences cardio-metabolic risk over time. A recent review on the longitudinal relationships of built environments with physical activity reported that environmental attributes measured at one point of time may not contribute to changes in physical activity [10]. People's behavior choice is known to be habitual, often triggered by environmental cues [56]. Given that this study focused on participants who stayed in the same residence, it is possible that increasing physical activity may require additional non-environmental stimuli, such as advice from health professionals, new incentives to use active modes of travel, and social pressure to exercise. Natural experimental studies examining changes in environments (due to relocation or environmental modification) are needed to explore the mediating role of physical activity changes in the environmental impacts on cardio-metabolic health. It is possible that the behavioral changes observed are attributable to environmental changes, which we could not measure in this study.

Limitations and strengths

Limitations of this study include the use of self-reported physical activity measures: measurement error may have resulted in incorrect estimations. The association observed between walkability and baseline physical activity may be confounded by self-selection of neighborhoods [57]. Neighborhood walkability is more closely related to transport-related walking [58], which is typically lower in intensity than exercise. However, inclusion of leisure-time physical activity and exercise may have contributed to weakening the relationship between walkability and total physical activity. Future research needs to examine the role of physical activity in specific domains and intensity levels. The attrition rate was relatively high due to the longer follow-up period (55%). Under the assumption of MAR mechanism, up to 60% loss to follow-up was less likely to produce biased estimates of effects [59]. However, if attrition was "missing not at random" (i.e., loss to follow-up depends on the outcome variable), the estimated effects may have been biased and led to invalid conclusions [59]. We used a walkability index that was created based on geospatial data sourced around the time of AusDiab3. This was due to the unavailability of relevant data for the baseline period (1999–2000). It is possible that some study areas may have changed little, while others may have undergone further development during the study period [60]. Future longitudinal research may have to consider how baseline and change in walkability can influence residents' cardio-metabolic risk.

Strengths of our study include sufficiently large sample size, longitudinal design with a 12-year follow-up period (three measurement points), the use of objective measures of cardio-metabolic risk markers, the use of GIS-based walkability measure, and a broad range of study areas from multiple urban settings across Australia. The study tested mediation following recent advancements in mediation analysis methods. We also used a sophisticated statistical method, multilevel growth model, in analyzing the complex data (repeated measures within individuals, who were recruited using stratified cluster sampling).

Conclusions

Our findings suggest that neighborhood environments designed to encourage residents' physical activity may help reduce the risk of obesity and related disease over time. Improving neighborhood walkability may be a potential strategy to enhance population health by encouraging more physical activity. Further studies are recommended to examine specific environmental attributes that may contribute to reducing cardio-metabolic risk (not only obesity but also hypertension, hyperglycemia, and hyperlipidemia) through physical activity. Such understanding would support policy-makers and practitioners in urban design and planning to develop healthier neighborhoods. Our study found an adverse effect of high walkability on blood lipids, suggesting the presence of other unhealthy exposures in high walkable areas. Research is needed to examine other behavioral pathways (e.g. diet) through which walkability may influence residents' cardio-metabolic health.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12966-019-0849-7.

Additional file 1: Table S1. Baseline characteristics of stayers, movers, and drop-outs, AusDiab study (1999-2012); Material S1. Active Australia Survey Items Used to Measure Physical Activity; Material S2. Calculating Changes Using Values Measured at Three Observation Points; Material S3. Details of the Three-Level Linear Growth Model Used in the Study

Abbreviations

2-h PG: 2-h Postload Plasma Glucose; AAS: Active Australia Survey; AusDiab: Australian Diabetes, Obesity and Lifestyle Study; CCD: Census Collector Districts; DBP: Diastolic Blood Pressure; FPG: Fasting Plasma Glucose; HDL-C: High-Density Lipoprotein Cholesterol; IRSD: Index of Relative Socioeconomic Disadvantage; MAR: Missing at Random; SBP: Systolic Blood Pressure; T2D: Type 2 Diabetes; TG: Triglycerides; WC: Waist Circumference

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Authors' contributions

MC and TS conceived of and designed the study. NO, BGC, GT, AC, and EC assisted in the conception and design of the study. MC conducted the spatial analysis with guidance from TS and SM. MC conducted the statistical analysis with guidance from EC. MC and TS wrote the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

Data that support the findings of this study are available on request under a license agreement. Written applications can be made to the AusDiab Steering Committee (Dianna.Magliano@baker.edu.au).

Ethics approval and consent to participate

The International Diabetes Institute and the Alfred Hospital Ethics Committee approved the study (approval no. 39/11). All participants provided written informed consent to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. WHO. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: World Health Organization; 2013.
2. Vasan RS, Benjamin EJ. The future of cardiovascular epidemiology. Circulation. 2016;133(25):2626–33.
3. Chandrabose M, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, et al. Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. Obes Rev. 2019;20(1):41–54.
4. den Braver NR, Lakerveld J, Rutters F, Schoonmade LJ, Brug J, Beulens JWJ. Built environmental characteristics and diabetes: a systematic review and meta-analysis. BMC Med. 2018;16(1):12.
5. Leal C, Chaix B. The influence of geographic life environments on cardiometabolic risk factors: a systematic review, a methodological assessment and a research agenda. Obes Rev. 2011;12(3):217–30.
6. Mackenbach JD, Rutter H, Compernolle S, Glonti K, Oppert JM, Charreire H, et al. Obesogenic environments: a systematic review of the association between the physical environment and adult weight status, the SPOTLIGHT project. BMC Public Health. 2014;14(1):233.
7. Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, et al. City planning and population health: a global challenge. Lancet. 2016;388(10062):2912–24.
8. Barnett DW, Barnett A, Nathan A, Van Cauwenberg J, Cerin E, Council on E, et al. Built environmental correlates of older adults' total physical activity and walking: a systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):103.
9. Cerin E, Nathan A, van Cauwenberg J, Barnett DW, Barnett A, Council on E, et al. The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):15.
10. Karmeniemi M, Lankila T, Ikaheimo T, Koivumaa-Honkanen H, Korpelainen R. The built environment as a determinant of physical activity: a systematic review of longitudinal studies and natural experiments. Ann Behav Med. 2018;52(3):239–51.
11. Van Cauwenberg J, Nathan A, Barnett A, Barnett DW, Cerin E, CEPA, et al. Relationships between neighbourhood physical environmental attributes and older adults' leisure-time physical activity: a systematic review and meta-analysis. Sports Med. 2018;48(7):1635–60.
12. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care. 2007;30(3):744–52.
13. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017;390(10113):2643–54.
14. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124(7):789–95.
15. Koohsari MJ, Kaczynski AT, Nakaya T, Shibata A, Ishii K, Yasunaga A, et al. Walkable urban design attributes and japanese older adults' body mass index: mediation effects of physical activity and sedentary behavior. Am J Health Promot. 2018;33(5):764–67.
16. Van Cauwenberg J, Van Holle V, De Bourdeaudhuij I, Van Dyck D, Deforche B. Neighborhood walkability and health outcomes among older adults: the mediating role of physical activity. Health Place. 2016;37:16–25.
17. Van Dyck D, Cerin E, Cardon G, Deforche B, Sallis JF, Owen N, et al. Physical activity as a mediator of the associations between neighborhood walkability and adiposity in Belgian adults. Health Place. 2010;16(5):952–60.
18. Gaesser GA, Angadi SS, Sawyer BJ. Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. Phys Sportsmed. 2011;39(2):87–97.
19. Carroll SJ, Niyonsenga T, Coffee NT, Taylor AW, Daniel M. Does physical activity mediate the associations between local-area descriptive norms, built environment walkability, and glycosylated hemoglobin. Int J Environ Res Public Health. 2017;14(9):953.

20. Hirsch JA, Diez Roux AV, Moore KA, Evenson KR, Rodriguez DA. Change in walking and body mass index following residential relocation: the multi-ethnic study of atherosclerosis. Am J Public Health. 2014;104(3):e49–56.
21. Hirsch JA, Moore KA, Barrientos-Gutierrez T, Brines SJ, Zagorski MA, Rodriguez DA, et al. Built environment change and change in BMI and waist circumference: multi-ethnic study of atherosclerosis. Obesity (Silver Spring). 2014;22(11):2450–7.
22. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173.
23. Cerin E, Mackinnon DP. A commentary on current practice in mediating variable analyses in behavioural nutrition and physical activity. Public Health Nutr. 2009;12(8):1182–8.
24. Preacher KJ. Advances in mediation analysis: a survey and synthesis of new developments. Annu Rev Psychol. 2015;66:825–52.
25. Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. Commun Monogr. 2009;76(4):408–20.
26. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods. 2002;7(1):83–104.
27. Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw JE, De Courten M, et al. The Australian diabetes, obesity and lifestyle study (AusDiab)—methods and response rates. Diabetes Res Clin Pract. 2002;57(2):119–29.
28. ABS. Statistical geography -Australian standard geographical classification (ASGC), digital boundaries, 2006 (cat. no. 1259.0.30.002). Canberra: Australian Bureau of Statistics; 2006.
29. Stessman J, Hammerman-Rozenberg R, Cohen A, Ein-Mor E, Jacobs JM. Physical activity, function, and longevity among the very old. Arch Intern Med. 2009;169(16):1476–83.
30. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research more common than imagined? Circulation. 2017;135(24):2369–72.
31. Frank LD, Sallis JF, Saelens BE, Leary L, Cain K, Conway TL, et al. The development of a walkability index: application to the neighborhood quality of life study. Br J Sports Med. 2010;44(13):924–33.
32. Mavoa S, Eagleson S, Badland HM, Gunn L, Boulange C, Stewart J, et al. Identifying appropriate land-use mix measures for use in a national walkability index. J Transp Land Use. 2018;11(1):681–700.
33. Forsyth A, Van Riper D, Larson N, Wall M, Neumark-Sztainer D. Creating a replicable, valid cross-platform buffering technique: the sausage network buffer for measuring food and physical activity built environments. Int J Health Geogr. 2012;11(1):14.
34. Millward H, Spinney J, Scott D. Active-transport walking behavior: destinations, durations, distances. J Transp Geogr. 2013;28:101–10.
35. ABS. Census of population and housing: mesh block counts, 2011 (cat. no. 2074). Canberra: Australian Bureau of Statistics; 2011.
36. Forsyth A, Koepp J, Larson N, Lytle L, Mishra N, Zimmerman J. NEAT-GIS protocols: neighborhood environment for active transport—Geographic Information Systems, Version 5.1 2012. New York; 2012. http://designforhealth.net/resources/other/gis-protocols/
37. Turrell G, Haynes M, Wilson L-A, Giles-Corti B. Can the built environment reduce health inequalities? A study of neighbourhood socioeconomic disadvantage and walking for transport. Health Place. 2013;19:89–98.
38. AIHW. The Active Australia Survey: A guide and manual for implementation, analysis and reporting: Australian Institute of Health and Welfare; 2003.
39. Armstrong T, Bauman AE, Davies J. Physical activity patterns of Australian adults: results of the 1999 National Physical Activity Survey: Australian Institute of Health and Welfare; 2000.
40. Brown W, Bauman A, Chey T, Trost S, Mummery K. Method: comparison of surveys used to measure physical activity. Aust N Z J Public Health. 2004; 28(2):128–34.
41. Timperio A, Salmon J, Crawford D. Validity and reliability of a physical activity recall instrument among overweight and non-overweight men and women. J Sci Med Sport. 2003;6(4):477–91.
42. ABS. Census of population and housing: Socio-economic indexes for areas (SEIFA), Australia (cat. no. 2033.0.55.001). Canberra: Australian Bureau of Statistics; 2011.
43. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol. 2011;62: 583–619.
44. Hox JJ. Multilevel analysis: techniques and applications. New York: Routledge; 2010.
45. Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001;30(3): 427–32.
46. UN. Sixty-seventh session Political Declaration of the High Level meeting of the General Assembly on the Prevention and control of non-communicable diseases. United Nations; 2011.
47. Sarkar C, Webster C, Gallacher J. Neighbourhood walkability and incidence of hypertension: findings from the study of 429,334 UK biobank participants. Int J Hyg Environ Health. 2018;221(3):458–68.
48. Braun LM, Rodriguez DA, Song Y, Meyer KA, Lewis CE, Reis JP, et al. Changes in walking, body mass index, and cardiometabolic risk factors following residential relocation: longitudinal results from the CARDIA study. J Transp Health. 2016;3(4):426–39.
49. Li F, Harmer P, Cardinal BJ, Vongjaturapat N. Built environment and changes in blood pressure in middle aged and older adults. Prev Med. 2009;48(3): 237–41.
50. Braun LM, Rodriguez DA, Evenson KR, Hirsch JA, Moore KA, Diez Roux AV. Walkability and cardiometabolic risk factors: cross-sectional and longitudinal associations from the multi-ethnic study of atherosclerosis. Health Place. 2016;39:9–17.
51. de Groot R, van den Hurk K, Schoonmade LJ, de Kort WL, Brug J, Lakerveld J. Urban-rural differences in the association between blood lipids and characteristics of the built environment: a systematic review and meta-analysis. BMJ Glob Health. 2019;4(1):e001017.
52. Tabaei BP, Rundle AG, Wu WY, Horowitz CR, Mayer V, Sheehan DM, et al. Associations of residential socioeconomic, food, and built environments with glycemic control in persons with diabetes in New York City from 2007-2013. Am J Epidemiol. 2018;187(4):736–45.
53. Minton J, Dimairo M, Everson-Hock E, Scott E, Goyder E. Exploring the relationship between baseline physical activity levels and mortality reduction associated with increases in physical activity: a modelling study. BMJ Open. 2013;3(10):6.
54. May AM, Bueno-de-Mesquita HB, Boshuizen H, Spijkerman AMW, Peeters PHM, Verschuren WMM. Effect of change in physical activity on body fatness over a 10-y period in the Doetinchem cohort study. Am J Clin Nutr. 2010;92(3):491–9.
55. Fogelholm M, Kukkonen-Harjula K. Does physical activity prevent weight gain – a systematic review. Obes Rev. 2000;1(2):95–111.
56. Marteau TM, Hollands GJ, Fletcher PC. Changing human behavior to prevent disease: the importance of targeting automatic processes. Science. 2012;337(6101):1492–5.
57. Boone-Heinonen J, Gordon-Larsen P, Guilkey DK, Jacobs DR Jr, Popkin BM. Environment and physical activity dynamics: the role of residential self-selection. Psychol Sport Exerc. 2011;12(1):54–60.
58. Giles-Corti B, Timperio A, Bull F, Pikora T. Understanding physical activity environmental correlates: increased specificity for ecological models. Exerc Sport Sci Rev. 2005;33(4):175–81.
59. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol. 2003;19(8):751–60.
60. Hirsch JA, Grengs J, Schulz A, Adar SD, Rodriguez DA, Brines SJ, et al. How much are built environments changing, and where?: patterns of change by neighborhood sociodemographic characteristics across seven US metropolitan areas. Soc Sci Med. 2016;169:97–105.

Publisher's Note

CHAPTER 6: GENERAL DISCUSSION

This Thesis aimed to advance the understanding of the potential impacts of the neighbourhood built environment on cardio-metabolic health among adults. This was achieved through a systematic review (Study One, the manuscript was reported in Chapter 2) and two empirical studies (Study Two and Study Three, the manuscripts were reported in Chapters 4 and 5, respectively). Each of these three studies has its own Discussion section that provided interpretations of the study findings, comparisons with existing studies in the literature, and descriptions of strengths and limitations. This final chapter draws together the key findings of these studies and discusses the implications of this body of research. It is organised into six sections. In the first section (6.1), an overview of the findings of each study is provided. The second section (6.2) synthesises these studies by comparing the findings of each specific study. The overall strengths and limitations of the Thesis are discussed in the third section (6.3). The fourth section (6.4) outlines potential future research directions. The implications of the Thesis findings for public health initiatives and urban planning policies are presented in the fifth section (6.5). The final section (6.6) concludes the Thesis.

6.1 Overview of the Findings

6.1.1 Study One: the systematic review

Study One was a systematic review and meta-analysis of longitudinal studies on the built environment and cardio-metabolic health. Previous systematic reviews on this topic mostly summarised findings of cross-sectional studies and focused largely on obesity-related outcomes (36, 37, 47). A new systematic review was conducted to synthesise evidence from longitudinal studies that examined a range of cardio-metabolic health outcomes (76). This systematic review summarised findings from 36 published articles. To quantify the strength of the evidence, the systematic review used a meta-analytic approach that accounted for the methodological quality of the studies reviewed. The key findings of the systematic review are presented in Figure 6.1.

	Potential to Reduce the Risk Over time		
	Obesity	**T2D** †	**Hypertension**
Higher **Walkability**	Strong evidence	Strong evidence	Very strong evidence
Lower **Urban Sprawl**	Strong evidence	–	–
Better Access to **Recreational Facilities**	Weak evidence	–	–
Better Access to **Destinations**	No evidence	–	–
Better **Route Attributes**	No evidence	–	–

Figure 6.1: Key Findings of the Systematic Review: Evidence for Potential Long-term Impacts of Built Environments on Cardio-metabolic Health
Note:† Type 2 diabetes; – insufficient studies to determine the strength of evidence

This systematic review of longitudinal studies identified that studies conducted to date have focused mostly on obesity-related outcomes; other risk factors related to T2D and hypertension were examined only in relation to walkability. Overall, the meta-analysis found strong evidence for potential long-term protective effects of higher walkability against the risk of obesity, type 2 diabetes (T2D), and hypertension. The meta-analysis also found strong evidence for a potential long-term impact of urban sprawl on obesity risk. There was weak evidence for a potential protective effect of better access to recreational facilities against obesity. No evidence was found for relationships of access to destinations (e.g., public transport stops, retail stores) or route attributes (e.g., street connectivity, traffic intensity) with obesity risk. In addition, there was inconclusive evidence for the mediating role of physical activity in the long-term impacts of the neighbourhood built environment on cardio-metabolic health.

6.1.2 Study Two: urban densification and cardio-metabolic risk

Study Two examined the potential impacts of neighbourhood population-density increases (densification) on changes in cardio-metabolic risk. This is the first known study to have examined the broader cardio-metabolic health impacts of densification. This study used

objective measures for population density and cardio-metabolic risk markers measured at three time points over a 12-year period. The study areas were diverse in population density change; ranging from -4.1% to 7.8% annually during the study period. The key findings of Study Two are presented in Figure 6.2.

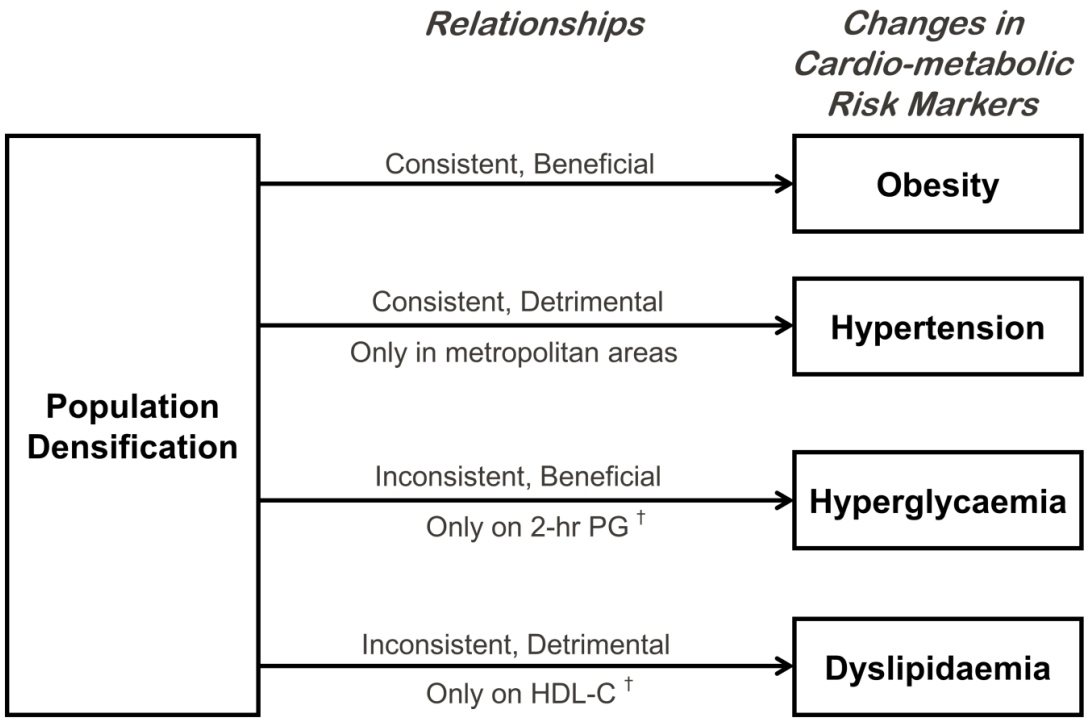


Figure 6.2: Key Findings of Study Two: Relationships between Population Densification and Changes in Cardio-metabolic Risk
Note: † 2-hr PG, 2-hour postload plasma glucose; HDL-C, high-density lipoprotein cholesterol

Higher levels of densification (both relative and absolute measures) were related to smaller increases in obesity markers (weight and waist circumference). Densification had adverse effects on changes in blood pressure measures, but these relationships were only consistently found in metropolitan areas. No consistent pattern was observed for relationships between densification and hyperglycaemia markers, with higher levels of densification (absolute measures) only related to smaller increases in 2-hour postload plasma glucose, but not with fasting plasma glucose. The results for dyslipidaemia markers were also mixed: higher levels of densification were detrimentally related to changes in high-density lipoprotein cholesterol, but not with triglycerides.

6.1.3 Study Three: walkability, cardio-metabolic risk, and the role of physical activity

Study Three examined the potential mediating role of physical activity in the relationships between neighbourhood walkability and changes in cardio-metabolic risk. The potential mediator, physical activity, was assessed by self-reported time spent in moderate-to-vigorous physical activity (including walking), at three time points over the 12-year period. The mediating roles of both baseline and 12-year change in physical activity were examined. The key findings of Study Three are presented in Figure 6.3 and Figure 6.4.

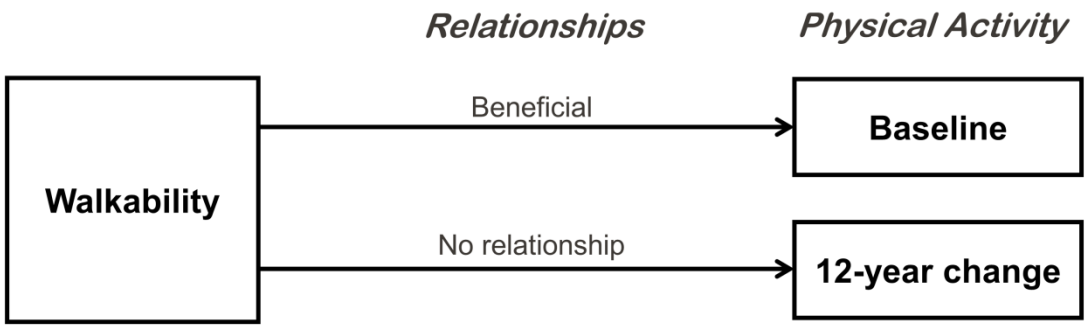


Figure 6.3: Key Findings of Study Three: Relationships of Walkability with Physical Activity

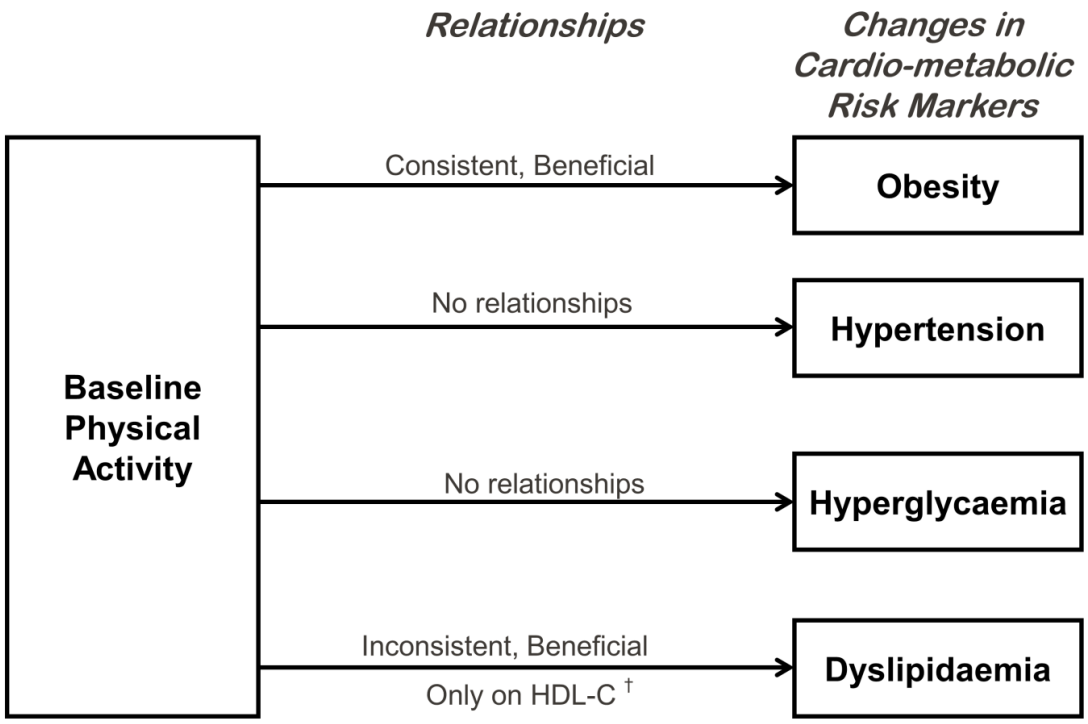


Figure 6.4: Key Findings of Study Three: Relationships of Baseline Physical Activity with Changes in Cardio-metabolic Risk. Note: † HDL-C, high-density lipoprotein cholesterol

Higher walkability was related to higher baseline physical activity levels but not with a change in physical activity. Baseline physical activity, in turn, was related to smaller increases in obesity markers (weight and waist circumference) and a greater increase in high-density lipoprotein cholesterol but was not related to changes in blood pressure or blood glucose measures.

6.2 Synthesis of the Overall Findings

Bringing together the findings of the three studies, it can be broadly understood that the neighbourhood built environment attributes are likely to have long-term effects on residents' cardio-metabolic health. The built environment features that the empirical studies of this Thesis focused are population density and walkability, which are posited to facilitate physical activity (28, 29). Given that regular physical activity participation is known to reduce cardio-metabolic risk (13, 15), these built environmental attributes can be postulated to confer cardio-metabolic health benefits over time. However, the findings of the two empirical studies suggest that densification and walkability may have both beneficial and adverse long-term effects on cardio-metabolic health. The following subsections synthesise findings for specific cardio-metabolic risk categories: obesity; hypertension; hyperglycaemia and type 2 diabetes; and dyslipidaemia.

6.2.1 Obesity

The systematic review and the two empirical studies consistently suggested that neighbourhood built environment features, which facilitate physical activity, are likely to have long-term protective effects against the risk of obesity.

The systematic review (Study One) found strong evidence for beneficial effects of composite built environmental indices (walkability, urban sprawl) against obesity risk over time (76). A previous systematic review reported that urban sprawl measures were consistently associated with body weight status, but mixed findings for the relationships between walkability and weight status (37). However, that systematic review mostly included cross-sectional studies and did not assess the strength of the evidence using a meta-analysis that accounted for methodological quality of the studies reviewed (37).

Given that Study One exclusively reviewed longitudinal studies and meta-analysed the study findings, it can be argued that living in neighbourhoods with higher walkability or lower urban sprawl may provide long-term protective effects against obesity.

Study Two found that, in the context of Australia, residents of neighbourhoods with higher densification levels were more likely to have smaller increases in obesity risk markers than those living in neighbourhoods with lower densification levels. Similar to these findings, a previous American study also found that an increase in population density, measured at larger geographical areas (metropolitan statistical area), was inversely related to an increase in body mass index over 30 years (77). Study Two along with this American study suggest potential long-term protective effects of population densification against obesity.

Study Three also observed relationships of higher walkability with smaller increases in obesity markers, which further adds to the evidence-base alongside Study One (76). This study also found that those relationships between walkability and obesity risk may be in part attributable to higher physical activity levels. Thus, this Thesis found evidence of physical activity as a behavioural mechanism through which walkability mitigates the risk of obesity over time, making an additional contribution to the literature.

6.2.2 Hypertension

The systematic review found strong evidence for potential long-term protective effects of neighbourhood walkability against hypertension risk, derived from studies with a follow-up period ranging from 1 to 7 years. Study Three, which examined the impacts of walkability on 12-year blood pressure changes, also noted smaller increases in systolic blood pressure for residents of high walkability neighbourhoods, relative to those of low walkability neighbourhoods (non-significant findings for diastolic blood pressure). Similar to Study Three, a recent study on walkability and hypertension risk conducted in the UK (78), which was not included in the systematic review, also found higher walkability to be related to smaller increases in systolic blood pressure but non-significant findings for diastolic blood pressure. It has been reported that systolic blood pressure can be a better predictor of hypertension, relative to other blood pressure measures (diastolic or pulse

pressure) (79). There was no evidence found to claim physical activity as the possible behavioural mechanism between walkability and blood pressure changes in Study Three. Nevertheless, this Thesis strengthened the evidence base by showing potential long-term protective effects of living in high walkability neighbourhoods against the risk of hypertension, with further research required to understand the mechanisms.

Importantly, population density increase was found to be related to greater increases in blood pressure in metropolitan areas. Given that population density is posited to facilitate physical activity (28), it was expected that densification would beneficially impact on blood pressure changes. It is not possible to explain the current findings within the scope of this Thesis. However, population density increases can involve various changes in neighbourhood environments, which were not investigated in this Thesis. They include increased motor vehicle traffic congestion, increased noise and air pollution, and reduced green space, some of which may contribute to increases in blood pressure. To disentangle the potential impacts of densification on hypertension risk, research examining multiple pathways is needed.

6.2.3 Hyperglycaemia and type 2 diabetes

The systematic review provided strong evidence for potential long-term protective effects of neighbourhood walkability against the risk of hyperglycaemia and T2D. Most studies in the systematic review examined the incidence of T2D rather than its markers. Another recent systematic review and meta-analysis (including both cross-sectional and longitudinal studies) also found that higher walkability was consistently associated with lower T2D prevalence/incidence (80). However, the systematic review of this Thesis (Study One) observed that studies which examined markers of T2D produced mixed findings. For instance, a study demonstrated that moving to higher walkability neighbourhoods was not related to a change in fasting plasma glucose in the USA (81), while another Australian study found that higher walkability was related to smaller increases in HbA_{1c} (another marker of T2D) (82). The empirical studies of this Thesis also produced inconsistent findings on walkability and blood glucose. Study Three found that higher walkability was related to smaller increases in fasting plasma glucose, but not with 2-hr postload plasma glucose. Study Three also did not find physical activity as a potential

mediator linking walkability and changes in blood glucose measures. In addition, Study Two found that population densification was related to smaller increases only in 2-hr postload plasma glucose, but not with fasting plasma glucose. Thus, it is observed that findings are consistent when studies examined a categorical T2D outcome (i.e., based on the cut-off for diagnosis), but findings are mixed when examining continuous risk maker changes. This warrants further investigations of the relationships between walkability and markers of T2D, including whether non-linear relationships exist.

6.2.4 Dyslipidaemia

The systematic review identified only a few studies examining potential long-term impacts of the built environment on the risk of dyslipidaemia. Three existing studies, examining the relationships between walkability and dyslipidaemia risk over time, produced mixed findings (81, 83, 84). Braun et al (81) found that moving to higher walkability neighbourhoods was related to a greater increase in triglycerides (i.e., an adverse effect), whereas the other two studies did not find relationships between walkability and the risk of dyslipidaemia. Study Two found that higher levels of population densification were related to smaller increases in high-density lipoprotein cholesterol (HDL-C), but not with triglycerides. Study Three also found that higher walkability levels were related to smaller increases in HDL-C, but not with triglycerides. Since HDL-C is inversely related to cardio-metabolic risk (85), these findings suggest that higher walkability and population densification would increase the risk of dyslipidaemia. On the contrary, Study Three found that higher walkability neighbourhoods were likely facilitating more physical activity, which was, in turn, related to a greater increase in HDL-C (i.e., a beneficial effect).

The potential adverse effects of walkability and population densification on dyslipidaemia observed in the empirical studies of this Thesis may be due to the availability of ‘unhealthy’ food outlets in higher walkable and higher densification neighbourhoods. In Study Three, a component used to calculate the walkability index was the density of ‘daily living destinations’, which included supermarkets and convenience stores. It may be possible that better access to these destinations can also mean better access to unhealthy food (characteristics of food sold in these destinations are unknown). Convenience stores, in particular, may carry foods that are high in trans-unsaturated fatty acids (e.g. snacks),

which are related to a reduction in HDL-C (86). However, given that the same walkability index was found to have potentially beneficial effects on other cardio-metabolic risk markers, further research is needed to understand why detrimental effects on blood lipid measures were observed for higher walkability and higher densification.

6.3 Strengths and Limitations

This Thesis investigated complex longitudinal relationships of built environment attributes with a broader range of cardio-metabolic risk outcomes. Its overall strengths and limitations are detailed below.

6.3.1 Strengths of the Thesis

6.3.1.1 *Systematic review*

This is the first known systematic review that exclusively reviewed longitudinal studies on the relationships between built environment attributes and a broader range of cardio-metabolic health outcomes in adults. This review quantified the strength of evidence using a meta-analytic approach that accounted for the methodological quality of the studies. The quality assessment tool evaluated relevant characteristics: study design, exposure variability, adjustment for individual and area-level confounding factors, longitudinal design characteristics, temporal match and measurement of built environmental exposures and cardio-metabolic outcomes. In particular, assessing the quality of built environment exposure measurement methods is a major strength of this systematic review (87).

6.3.1.2 *Source of data for empirical studies*

The two empirical studies of this Thesis used longitudinal data from the AusDiab study. In this study, data were collected at three waves over a 12-year follow-up period. Participants were recruited from a range of urban settings across Australia, which increases the variability of environmental measures and makes the study findings more generalisable in the context of Australia, in comparison to previous studies conducted in a single metropolitan city. The use of eight cardio-metabolic risk markers measured through

standard biomedical protocols was another strength of this Thesis. The two empirical studies included sufficiently large sample sizes (> 2,000) from the AusDiab study data.

6.3.1.3 *Spatial analysis*

A large proportion of the time devoted to this PhD research was spent in the preparation and cleaning of geospatial data, followed by calculation and validation of built environment attributes for AusDiab participants. The AusDiab study collected data in multiple regions across Australia. Thus, national-level retrospective geospatial datasets, corresponding to the three data collection periods, were required to create concordant neighbourhood built environment measures for study participants. This process was assisted by the Centre for Research Excellence (CRE) in Healthy, Liveable Communities, of which the candidate is a member (88). High-quality retrospective national geospatial data available in the CRE were used to calculate environmental attributes in this Thesis. The current best practice was used in the process of GIS operations with guidance from GIS experts in the CRE team. For instance, participants' residential addresses were geocoded using two different approaches and validated for location accuracy. Participants' neighbourhoods were defined by individual buffers, as they are more likely to capture local areas of residents as opposed to administrative units, which may not necessarily be aligned with participants' neighbourhoods (53).

6.3.1.4 *Statistical analysis*

The AusDiab data has a multi-level structure due to the two-stage stratified cluster sampling and longitudinal data collection. Multilevel linear growth models were used in regression analyses to account for both the dependence between repeated measures within participants and the spatial clustering within study areas. Study Three assessed the potential mediating effects of physical activity using the joint-significance test in response to a research gap identified in the systematic review, i.e., existing longitudinal studies on this topic, for the most part, used a traditional mediation analysis approach (i.e., Barron and Kenny's approach) (89) that can provide incorrect findings. A study reported that the joint-significance test achieves the best balance of low Type I Error and the high statistical power to detect a true mediating effect among a number of other methods compared (75).

6.3.2 Limitations of the Thesis

6.3.2.1 *Response rate, follow-up rate and selection bias*

The baseline response rate of the AusDiab study was 55.3%. Compared with the general Australian population at baseline, females and middle-to-older adults aged over 45 years were over-represented among respondents (56). The 12-year follow-up rate was 44.6%. For the analytical sample, participants who relocated during the study period were excluded. Differences were observed between those who were included in the analytical sample (stayers), those who were excluded (movers), and those who withdrew (dropped-outs) in relation to some of their baseline socio-demographic and health characteristics. Those characteristics were adjusted in the regression analyses, adhering to 'traditional' methods of dealing with confounding bias (90, 91). However, further sensitivity analyses, using 'counterfactual' methods such as propensity score matching, were not conducted to assess the impact of the response rate, loss to follow-up, and selection bias on study findings (91).

6.3.2.2 *Challenges in obtaining retrospective geospatial data*

It was found that geospatial data available for the baseline study period (1999–2000) were highly limited. Study Two used population density changes partly because the corresponding data were available from Census data aligning with the three AusDiab study data collection points (66, 67). The exposure for Study Three was walkability, for which a wide range of geospatial data (density, diversity and design) are necessary. More recent geospatial data corresponding to AusDiab3 (2011–12) were used in Study Three due to the unavailability of relevant data for AusDiab1 or AusDiab2. It is unknown whether walkability changed substantially during the study period, which may have affected the results of Study Three.

6.3.2.3 *Self-reported measures of physical activity*

To assess the mediation by physical activity in Study Three, self-reported total time spent in moderate- and vigorous-intensity physical activity (including walking) was assessed. The questionnaire items used to ask physical activity durations were derived from the Active Australia Survey, which has been shown to have acceptable levels of reliability and

validity (70, 71). However, self-reported measures of physical activity are known to involve recall error and bias (92), which may have affected the results of Study Three.

6.3.2.4 *Generalisability of findings*

Since AusDiab collected data from diverse urban settings within Australia, the findings empirical studies of this Thesis may be generalisable to urban areas of Australia. However, the findings of the empirical studies as well as the findings of the systematic review (as all studies reviewed were conducted in Western countries) may not be applicable to other localities, in particular, high-density Asian cities.

6.3.2.5 *Study design limitations*

This Thesis focused on longitudinal observational studies. In comparison to cross-sectional observational studies, which are predominant in the current body of evidence on built environment and health, longitudinal observational studies provide a better understanding of potential causal relationships by establishing "temporal ordering" between environmental exposures and health outcomes (41). However, longitudinal observational studies do also have important limitations in making causal inferences. Residential self-selection (i.e., healthy people may choose to live in environments supportive of physical activity) is a potential confounder of the relationship between built environment attributes and cardio-metabolic health outcomes in observational studies (42). Since in AusDiab study participants were not asked about their reasons for choosing their current residential location at baseline, it was not possible to adjust for self-selection in Study Two and Study Three. However, a US study found the effect of built environment changes on walking behaviour changes even after adjusting for preferences for neighbourhood characteristics or attitudes toward travel modes (93). It is also worth pointing out that empirical studies of this thesis analysed data only of those who stayed in the same residence for over 10 years. It can be argued that the confounding due to residential self-selection in these empirical studies may not be substantial when compared to shorter term studies or those involving movers.

As discussed in Chapter 2 (section 2.1.2), it is unfeasible to conduct experimental studies in which participants are randomly assigned to different levels of built environmental exposures. Quasi-experimental studies or natural experiments where participants are exposed to changes in the built environment (either through the construction of new infrastructure or through residential relocation) are more practical approaches. Further discussion on the importance of implementing quasi-experimental studies is provided in section 6.4.6.

6.4 Future Research Directions

6.4.1 Examining diverse built environment attributes

As identified in the Systematic Review, there are a relatively large number of studies examining the impacts of composite measures (such as walkability) on cardio-metabolic health outcomes. However, less research has been carried out on specific environmental attributes. In particular, examining long-term health impacts of specific built environment attributes (e.g., population/residential density, street connectivity, land use mix, destinations accessibility) may be useful to identify the 'dose' of interventions required to provide cardio-metabolic health benefits. Other specific environmental attributes such as public open space (parks, recreational facilities) and pedestrian infrastructure (e.g., availability of sidewalks and bicycle lanes, presence of street trees and crossing signals) could also be further considered. Examining these environmental features is worthwhile particularly in established neighbourhoods, as they may be easier to modify compared with structural components such as population density and street connectivity.

Investigating perceived built environmental characteristics may complement studies using objective measures. Perceptions are relevant because some environmental factors such as aesthetics and sense of safety are difficult to assess objectively. In addition, the systematic review found that perceived walkability may be more strongly related to health outcomes (i.e. attenuation in the strength of evidence after excluding perceived measures). A potential reason for such a finding is that participants' daily behaviours take place in their perceived neighbourhoods. A longitudinal study reported a mismatch between perceived and objectives measures of walkability in relationship with weight gain (94). However, in

a recent study, Cerin et al (95), using data from 14 cities across 10 countries, found that the relationship of certain objective built environmental characteristics with physical activity was mediated by their conceptually-comparable perceived indicators. Thus, investigating both objective and perceived environmental characteristics may help to better understand the relationships between the built environment, physical activity, and cardio-metabolic health outcomes.

6.4.2 Investigating broader cardio-metabolic health outcomes

The systematic review found that most studies conducted to date examined obesity-related outcomes. It is important to further investigate the relationships of built environments with a range of cardio-metabolic health outcomes including the biomedical risk factors and their markers, disease incidence, and mortality. In addition, examinations of clustered cardio-metabolic risk indices, calculated using multiple risk markers (96), are advantageous to better understand the impacts of the built environment on overall cardio-metabolic risk.

6.4.3 Defining neighbourhoods

How to define a neighbourhood, within which environmental attributes are calculated, is a key consideration in studies on built environments, physical activity and health outcomes. Empirical studies of this Thesis employed 1-km straight-line and street-network buffers around home as the relevant spatial units for 'neighbourhoods', with a rationale that this was shown to be a typical distance within which most neighbourhood walking trips take place among adults (65). However, the "modifiable areal unit problem" (MAUP) implies that different buffer types and scales may produce different relationships between environmental attributes and outcomes (97). As there is no known solution to MAUP, future studies can test whether study findings differ for different neighbourhood types and scales.

Another issue in defining neighbourhoods is the "uncertain geographic context problem" (UGCoP) (98). The size and shape of neighbourhoods depend to some extent on behaviours of interest as well as the spatial realities of where participants travel (99). This suggests that there are uncertainties in using a single buffer to determine any individual's

applicable neighbourhood. Assessing environmental attributes within an "activity space", which is defined by locations visited by participants and the routes connecting them, may overcome the issue of UGCoP (98). One approach to delineate an "activity space" is the use of Global Positioning System (GPS) devices, which can accurately capture where participants travel during the study period (53). Considering that defining a buffer within which environmental attributes are calculated is the fundamental step in research on the built environment and health, and different spatial units produce distinct results for their associations (100), future studies need to consider employing multiple methods in defining neighbourhoods to produce more robust evidence.

6.4.4 Investigating non-linear relationships and thresholds

This Thesis examined linear relationships between built environmental attributes and cardio-metabolic risk. However, it should be noted that non-significant linear relationships may be due to the presence of non-linear relationships, rather than no relationships at all. It is, thus, important to further investigate if meaningful and interpretable non-linear relationships can be found. Such investigations may even be useful to find any threshold values of built environment attributes that may provide optimal cardio-metabolic health benefits.

For instance, it has been previously hypothesised that certain population density may have non-linear relationships with physical activity (101). A comparative study found that better access to destinations was related to a higher likelihood of walking in Brisbane (a low-density city), whereas better access to destinations was associated with a lower amount of walking in Hong Kong (a high-density city), where better access may mean very short distances to destinations (102). Similarly, such non-linear associations may be applicable to the relationship between population density and cardio-metabolic risk. Figure 6.5 depicts a hypothesised non-linear relationship between population density and overall cardio-metabolic risk.

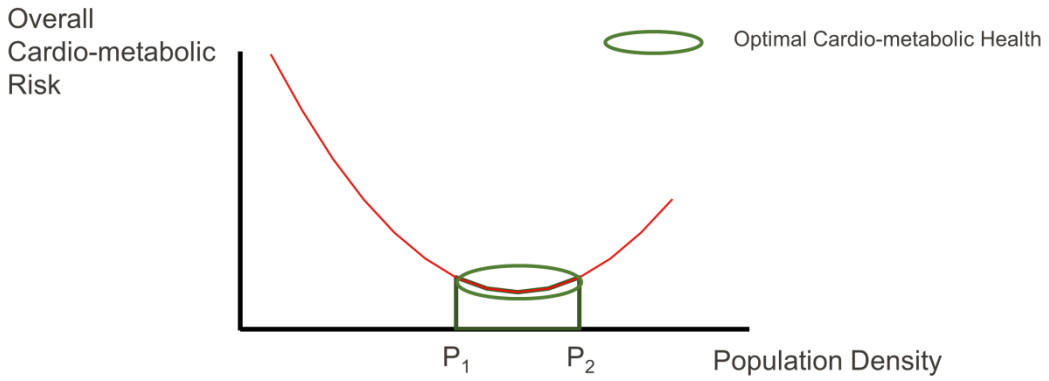


Figure 6.5: A Hypothesised Relationship between Population Density and Overall Cardio-metabolic Risk

Low-density neighbourhoods (population density < P_1) have limited access to destinations. On the other end, very high-density neighbourhoods (population density > P_2) may have access to destinations at shorter distances. Thus, both ends of population density would result in lower levels of physical activity (101). In addition, higher density neighbourhoods may also have other factors that may have adverse effects on health, such as higher traffic congestion, higher levels of air and noise pollution, poorer access to green spaces, and better access to unhealthy food destinations (103). Ideally, there would be a range of population density values (P_1 – P_2) that provide optimal cardio-metabolic health benefits without incurring adverse effects. Investigating whether such population density thresholds exist is a future research topic.

6.4.5 Assessing multiple pathways

The mechanisms through which the built environment affects residents' cardio-metabolic health are complex, with physical activity as just one of many pathways (38). Other potential pathways include behaviours (e.g., diet, sedentary behaviour) and environmental risk exposures (e.g., air and noise pollution) (38). Future studies should examine multiple potential pathways between the built environment and cardio-metabolic health outcomes.

An issue when examining multiple potential mediators is the use of an appropriate statistical mediation analysis method. Examining a single mediator individually without taking account of confounding of other potential mediators may result in inaccurate findings (54). Statistical methods, such as Structural Equation Models (SEMs), can be used

to assess multiple mediating effects when assumptions about linearity and normality hold for all variables in models (104). Advancements in statistical methods are currently underway in which multiple mediating effects can be assessed in multilevel regression models with non-normal (e.g. binary, counts, right skewed) variables in models (54). Application of such statistical methods in studies on the built environment and cardio-metabolic health helps to better understand the mechanisms between them.

6.4.6 Implementing quasi-experimental study designs

Most studies examining the built environmental impact on cardio-metabolic risk were observational in design. The next step towards making causal inference could be to implement quasi-experimental designs (43). To date, only one known study on this topic used a natural experiment (one type of quasi-experiment); it examined the impacts of relocation to areas with different levels of urban sprawl on the obesity risk among those who were displaced (with little to no control over their neighbourhood placement) after Hurricane Katrina in the USA (105). There are quasi-experimental studies that examined changes in physical activity due to infrastructure changes such as a park refurbishment (106), a public transit construction (107), or an urban greenway instalment (108). Similarly, there are quasi-experimental studies such as the Australian RESIDE study, which examined the changes in physical activity due to relocating to new housing developments with infrastructure supportive/unsupportive of physical activity (109). Future quasi-experimental studies should also examine changes in cardio-metabolic health outcomes due to neighbourhood infrastructure changes or relocations to planned housing developments.

6.4.7 Linking food environments and walkability

This Thesis found some unexpected results, such as walkability and population densification being adversely related to changes in blood lipid measures. It was speculated that the availability of destinations selling unhealthy food in higher walkability/densifying neighbourhoods may be a potential reason for such findings. Future research might consider examining the spatial co-location of walkable neighbourhoods and unhealthy food outlets to investigate their independent and joint effects on cardio-metabolic health.

6.4.8 Analysing subgroups

Individual demographic and socioeconomic factors (e.g., age, gender, education, income) are determinants of cardio-metabolic health (110), and may also influence individuals' decisions about where to live (45). In addition, area-level factors, such as neighbourhood socioeconomic disadvantage, are also known to be determinants of cardio-metabolic health (111), and related to local built environment factors (38). These may suggest that the way neighbourhood environments affect cardio-metabolic health may differ between subgroups. Future research needs to identify subgroups in which the built environment affects health outcomes differently, as examining them separately can help to assess the effects more accurately.

6.4.9 Conducting studies in non-Western countries

The systematic review found that all longitudinal studies reviewed were conducted in Western countries, typically in North America, Europe, and Australia. A number of cross-sectional studies have been conducted in non-Western countries such as China or Japan (112, 113). However, these studies mostly examined obesity-related outcomes. There is a need to examine longitudinal relationships of built environment attributes with a broader range of cardio-metabolic health outcomes in such settings, where environmental characteristics and behavioural patterns may be different from the countries where existing studies have been conducted.

6.4.10 Conducting policy-relevant research

Research findings are more useful to policymakers when scientific research is targeted to strategic policy goals (114). For instance, there are numerous studies examining the impacts of specific urban planning policy based measures of built environment attributes on physical activity (115). Little attention has been given to examining the impacts of such measures on cardio-metabolic health outcomes (116). Future research examining the effect of potentially relevant urban planning policies, such as smart growth, urban growth boundary policy, and green city, on cardio-metabolic health is warranted.

6.5 Implications for Public Health Initiatives and Urban Planning Policies

This section discusses the implications of the findings of this Thesis to policy and practice in public health and urban planning.

6.5.1 Public health initiatives

Globally and nationally, leading public health organisations advocate the importance of creating environments that support active living to reduce the population-level risk of cardio-metabolic diseases. The World Health Organization's 'Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) 2013-2020' recognises the need *'to reduce modifiable risk factors for non-communicable diseases and underlying social determinants through creation of health-promoting environments'* (1). The National Heart Foundation of Australia has developed a '*Blueprint for an Active Australia*' report, in which it stresses the importance of built environments to support active living to reduce the burden of cardiovascular and related diseases in Australia (117). The findings of this Thesis provide further justification for such public health initiatives by providing 'state-of-the-art' synthesis of current knowledge and more robust empirical evidence regarding the impacts of neighbourhood built environments on cardio-metabolic health. More specifically, the key messages of this Thesis to public health sectors are:

- Living in higher walkability neighbourhoods, where active living is supported, is likely to help residents in reducing the risk of cardio-metabolic diseases over time;
- Population density increases (densification), which is happening across many cities worldwide due to the global trends of urbanisation, is likely to have protective effects against obesity; however, densification may also have adverse cardio-metabolic health effects (i.e., elevating hypertension risk), which requires monitoring and understanding; and
- Physical activity participation is a potential behavioural mechanism that can explain protective effects of higher walkability against obesity.

6.5.2 Urban planning policies

This Thesis also has implications for urban planning policies and practices. In particular, population density is determined by urban planning policies (118). Study Two found that

densification is likely to have protective effects on the risk of obesity. This suggests that allowing more people to live in a neighbourhood is likely to be a promising strategy for helping to reduce the burden of obesity in the context of Australia. Major cities across Australia (both capital cities and other regional cities) are experiencing population increases (119). However, population increases do not automatically translate into population densification, if cities accommodate inhabitants by expanding the urban growth boundaries. In order to achieve optimal health benefits, cities need to have urban planning policies that restrict urban sprawl and promote higher density mixed-use development: in short, cities should be made up of walkable neighbourhoods. However, this Thesis also found potential adverse cardio-metabolic health impacts of densification. Thus, caution needs to be exercised when implementing densification strategies in urban settings in order to achieve optimal health benefits.

6.6 Conclusions

In conclusion, this Thesis expands the current knowledge regarding the potential long-term impacts of built environments on cardio-metabolic health. Research on built environment and cardio-metabolic health has relied mostly on evidence from cross-sectional studies, with some emerging evidence from longitudinal studies. This Thesis systematically reviewed longitudinal studies and synthesized the research evidence. Employing cutting-edge spatial and statistical analyses methods, two empirical studies were conducted to address the gaps identified in the review. Broadly, the systematic review found strong evidence for potential long-term protective effects of living in walkable neighbourhoods against the risk of obesity, hypertension, and type 2 diabetes, which were partly supported by empirical research. However, there are complexities in the relationships between built environments and cardio-metabolic health. Given the global context of rapid urbanisation and a growing interest in creating environment that support active living to reduce the burden of chronic diseases, there is an urgent need for further research addressing gaps in the literature, including examining joint effects of multiple environmental exposures and investigating whether any threshold values of built environment attributes would exist that provide optimal cardio-metabolic health benefits. Such investigations could assist researchers, policy-makers, and practitioners involved in public health and urban planning

to develop strategies to maximise the overall health benefits and minimise potential harms of environmental interventions.

REFERENCES

1. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva, Switzerland; 2013.
2. World Health Organization. Global health observatory (GHO) data: The top 10 causes of death. Geneva, Switzerland; 2018.
3. Australian Bureau of Statistics. National health survey: first results, 2017-18 (cat. No. 4364.0.55.001). Canberra, Australia; 2018.
4. Nichols M, Peterson K, Herbert J, Alston L, Allender S. Australian heart disease statistics 2015. Melbourne: National Heart Foundation of Australia; 2016.
5. Australian National Preventive Health Agency. State of preventive health 2013. Canberra, Australia; 2013.
6. Australian Institute of Health and Welfare. Evidence for chronic disease risk factors: Behavioural and biomedical risk factors (Cat. no: WEB 166). Canberra, Australia; 2016.
7. Fisher M. Cardiometabolic disease: the new challenge? Practical Diabetes. 2006;23(3):95-7.
8. Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol. 2008;28(6):1039-49.
9. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32-8.
10. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. Lancet. 2014;384(9937):45-52.
11. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.
12. World Health Organization. Global strategy on diet, physical activity and health. Geneva, Switzerland; 2004.
13. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2016;39(11):2065-79.

14. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017;390(10113):2643-54.
15. Sattelmair J, Pertman J, Ding EL, Kohl HW, 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124(7):789-95.
16. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29.
17. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380(9838):247-57.
18. Australian Institute of Health and Welfare. Healthy Communities: Health risk factors in 2014–15 – Insufficient physical activity. (Cat. no. HPF 6). Canberra, Australia; 2017.
19. Kohl HW, 3rd, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;380(9838):294-305.
20. Marcus BH, Williams DM, Dubbert PM, Sallis JF, King AC, Yancey AK, et al. Physical activity intervention studies: what we know and what we need to know: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); Council on Cardiovascular Disease in the Young; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation. 2006;114(24):2739-52.
21. Tudor-Locke C, Bell RC, Myers AM, Harris SB, Ecclestone NA, Lauzon N, et al. Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. Int J Obes Relat Metab Disord. 2004;28(1):113-9.
22. Schilling JM, Giles-Corti B, Sallis JF. Connecting active living research and public policy: transdisciplinary research and policy interventions to increase physical activity. J Public Health Policy. 2009;30 Suppl 1:S1-15.

23. Sallis JF, Owen N. Ecological models of health behavior. In: Glanz K, Rimer BK, Viswanath K, editors. Health behavior: Theory, research, and practice. 5. San Francisco: Jossey-Bass; 2015. p. 43-64.
24. Saelens BE, Handy SL. Built environment correlates of walking: a review. Med Sci Sports Exerc. 2008;40(7 Suppl):S550-66.
25. Wicker AW. An introduction to ecological psychology. Monterey, CA: Brooks Cole Publishing; 1979.
26. Marteau TM, Hollands GJ, Fletcher PC. Changing human behavior to prevent disease: the importance of targeting automatic processes. Science. 2012;337(6101):1492-5.
27. Karmeniemi M, Lankila T, Ikaheimo T, Koivumaa-Honkanen H, Korpelainen R. The built environment as a determinant of physical activity: a systematic review of longitudinal studies and natural experiments. Ann Behav Med. 2018;52(3):239-51.
28. Cervero R, Kockelman K. Travel demand and the 3Ds: density, diversity, and design. Transportation Research Part D-Transport and Environment. 1997;2(3):199-219.
29. Frank LD, Sallis JF, Saelens BE, Leary L, Cain K, Conway TL, et al. The development of a walkability index: application to the Neighborhood Quality of Life Study. Br J Sports Med. 2010;44(13):924-33.
30. Barnett DW, Barnett A, Nathan A, Van Cauwenberg J, Cerin E, Council on E, et al. Built environmental correlates of older adults' total physical activity and walking: a systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):103.
31. Cerin E, Nathan A, van Cauwenberg J, Barnett DW, Barnett A, Council on E, et al. The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):15.
32. McCormack GR, Shiell A. In search of causality: a systematic review of the relationship between the built environment and physical activity among adults. Int J Behav Nutr Phys Act. 2011;8:125.
33. Van Cauwenberg J, Nathan A, Barnett A, Barnett DW, Cerin E, Council on E, et al. Relationships between neighbourhood physical environmental attributes and older adults' leisure-time physical activity: a systematic review and meta-analysis. Sports Med. 2018;48(7):1635-60.

34. Sugiyama T, Neuhaus M, Cole R, Giles-Corti B, Owen N. Destination and route attributes associated with adults' walking: a review. Med Sci Sports Exerc. 2012;44(7):1275-86.
35. Vasan RS, Benjamin EJ. The future of cardiovascular epidemiology. Circulation. 2016;133(25):2626-33.
36. Leal C, Chaix B. The influence of geographic life environments on cardiometabolic risk factors: a systematic review, a methodological assessment and a research agenda. Obes Rev. 2011;12(3):217-30.
37. Mackenbach JD, Rutter H, Compernolle S, Glonti K, Oppert JM, Charreire H, et al. Obesogenic environments: a systematic review of the association between the physical environment and adult weight status, the SPOTLIGHT project. BMC Public Health. 2014;14(1):233.
38. Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, et al. City planning and population health: a global challenge. Lancet. 2016;388(10062):2912-24.
39. Booth KM, Pinkston MM, Poston WS. Obesity and the built environment. J Am Diet Assoc. 2005;105(5 Suppl 1):S110-7.
40. Giles-Corti B, Macintyre S, Clarkson JP, Pikora T, Donovan RJ. Environmental and lifestyle factors associated with overweight and obesity in Perth, Australia. Am J Health Promot. 2003;18(1):93-102.
41. Saelens BE, Sallis JF, Black JB, Chen D. Neighborhood-based differences in physical activity: an environment scale evaluation. Am J Public Health. 2003;93(9):1552-8.
42. Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. Relationship between urban sprawl and physical activity, obesity, and morbidity. Am J Health Promot. 2003;18(1):47-57.
43. Schmidt NM, Nguyen QC, Osypuk TL. Experimental and quasi-experimental designs in neighborhood health effects research: strengthening causal inference and promoting translation. Neighborhoods and Health. 2 ed. New York: Oxford University Press; 2018.
44. Sedgwick P. STATISTICAL QUESTION Cross sectional studies: advantages and disadvantages. BMJ-British Medical Journal. 2014;348:2.

45. Boone-Heinonen J, Gordon-Larsen P, Guilkey DK, Jacobs DR, Jr., Popkin BM. Environment and physical activity dynamics: the role of residential self-selection. Psychol Sport Exerc. 2011;12(1):54-60.
46. Taris TW. A primer in longitudinal data analysis: Sage; 2000.
47. Ding D, Gebel K. Built environment, physical activity, and obesity: what have we learned from reviewing the literature? Health & place. 2012;18(1):100-5.
48. Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. The built environment and obesity. Epidemiol Rev. 2007;29:129-43.
49. Black JL, Macinko J. Neighborhoods and obesity. Nutr Rev. 2008;66(1):2-20.
50. Feng J, Glass TA, Curriero FC, Stewart WF, Schwartz BS. The built environment and obesity: a systematic review of the epidemiologic evidence. Health Place. 2010;16(2):175-90.
51. Hirsch JA, Grengs J, Schulz A, Adar SD, Rodriguez DA, Brines SJ, et al. How much are built environments changing, and where?: Patterns of change by neighborhood sociodemographic characteristics across seven U.S. metropolitan areas. Soc Sci Med. 2016;169:97-105.
52. Gullón P, Lovasi GS. Designing healthier built environments. Neighborhoods and Health. 2 ed. New York: Oxford University Press; 2018.
53. Duncan DT, Regan SD, Chaix B. Operationalizing neighborhood definitions in health research: spatial misclassification and other issues. Neighborhoods and Health. 2 ed. New York: Oxford University Press; 2018.
54. VanderWeele TJ. Mediation analysis: a practitioner's guide. Annu Rev Public Health. 2016;37:17-32.
55. Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw JE, De Courten M, et al. The Australian diabetes, obesity and lifestyle study (AusDiab)—methods and response rates. Diabetes Res Clin Pract. 2002;57(2):119-29.
56. Dunstan DW, Zimmet PZ, Welborn TA, Sicree R, Armstrong T, Atkins R, et al. The Australian diabetes, obesity and lifestyle study 1999/2000 Report Melbourne, Australia: International Diabetes Institute; 2001.
57. Barr ELM, Magliano DJ, Zimmet PZ, Polkinghorne KR, Atkins RC, Dunstan DW, et al. The Australian diabetes, obesity and lifestyle study 2004/2005 Report. Melbourne, Australia: International Diabetes Institute; 2006.

58. Tanamas S, Magliano D, Lynch B, Sethi P, Willenberg L, Polkinghorne K, et al. TheAustralian diabetes, obesity and lifestyle study 2011/2012 Report. Melbourne, Australia: Baker IDI Heart and Diabetes Institute; 2013.
59. Australian Bureau of Statistics. Statistical geography -Australian standard geographical classification (ASGC), digital boundaries, 2006 (cat. no. 1259.0.30.002). Canberra, Australia; 2006.
60. Vine MF, Degnan D, Hanchette C. Geographic information systems: their use in environmental epidemiologic research. Environ Health Perspect. 1997;105(6):598-605.
61. Svennerberg G. Beginning Google maps API 3: Apress; 2010.
62. Jacquez GM. A research agenda: does geocoding positional error matter in health GIS studies? Spat Spatiotemporal Epidemiol. 2012;3(1):7-16.
63. DuVander A. Map scripting 101: an example-driven guide to building interactive maps with Bing, Yahoo!, and Google Maps: No Starch Press; 2010.
64. Forsyth A, Van Riper D, Larson N, Wall M, Neumark-Sztainer D. Creating a replicable, valid cross-platform buffering technique: the sausage network buffer for measuring food and physical activity built environments. Int J Health Geogr. 2012;11(1):14.
65. Millward H, Spinney J, Scott D. Active-transport walking behavior: destinations, durations, distances. J Transp Geogr. 2013;28:101-10.
66. Australian Bureau of Statistics. Mesh blocks digital boundaries, Australia, 2006 (cat. no. 209.0.55.002) Canberra, Australia; 2008.
67. Australian Bureau of Statistics. Census of population and housing: mesh block counts, 2011 (cat. no. 2074) Canberra, Australia; 2011.
68. Mavoa S, Eagleson S, Badland HM, Gunn L, Boulange C, Stewart J, et al. Identifying appropriate land-use mix measures for use in a national walkability index. Journal of Transport and Land Use. 2018;11(1).
69. Armstrong T, Bauman AE, Davies J. Physical activity patterns of Australian adults: results of the 1999 national physical activity survey: Australian Institute of Health and Welfare; 2000.

70. Brown W, Bauman A, Chey T, Trost S, Mummery K. Method: comparison of surveys used to measure physical activity. Aust N Z J Public Health. 2004;28(2):128-34.
71. Timperio A, Salmon J, Crawford D. Validity and reliability of a physical activity recall instrument among overweight and non-overweight men and women. J Sci Med Sport. 2003;6(4):477-91.
72. Australian Bureau of Statistics. Census of population and housing: Socio-economic indexes for areas (SEIFA), Australia (cat. no. 2033.0.55.001). Canberra, Australia; 2011.
73. Hox JJ. Multilevel analysis: techniques and applications. New York, United States: Routledge; 2010.
74. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol. 2011;62:583-619.
75. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods. 2002;7(1):83-104.
76. Chandrabose M, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, et al. Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. Obes Rev. 2019;20(1):41-54.
77. Zhao Z, Kaestner R. Effects of urban sprawl on obesity. J Health Econ. 2010;29(6):779-87.
78. Sarkar C, Webster C, Gallacher J. Neighbourhood walkability and incidence of hypertension: Findings from the study of 429,334 UK Biobank participants. Int J Hyg Environ Health. 2018;221(3):458-68.
79. Strandberg TE, Pitkala K. What is the most important component of blood pressure: systolic, diastolic or pulse pressure? Curr Opin Nephrol Hypertens. 2003;12(3):293-7.
80. den Braver NR, Lakerveld J, Rutters F, Schoonmade LJ, Brug J, Beulens JWJ. Built environmental characteristics and diabetes: a systematic review and meta-analysis. BMC Med. 2018;16(1):12.
81. Braun LM, Rodriguez DA, Evenson KR, Hirsch JA, Moore KA, Diez Roux AV. Walkability and cardiometabolic risk factors: Cross-sectional and longitudinal

associations from the Multi-Ethnic Study of Atherosclerosis. Health Place. 2016;39:9-17.

82. Carroll SJ, Niyonsenga T, Coffee NT, Taylor AW, Daniel M. Does physical activity mediate the associations between local-area descriptive norms, built environment walkability, and glycosylated hemoglobin? Int J Environ Res Public Health. 2017;14(9):953.
83. Paquet C, Coffee NT, Haren MT, Howard NJ, Adams RJ, Taylor AW, et al. Food environment, walkability, and public open spaces are associated with incident development of cardio-metabolic risk factors in a biomedical cohort. Health Place. 2014;28:173-6.
84. Braun LM, Rodriguez DA, Song Y, Meyer KA, Lewis CE, Reis JP, et al. Changes in walking, body mass index, and cardiometabolic risk factors following residential relocation: Longitudinal results from the CARDIA study. J Transp Health. 2016;3(4):426-39.
85. Rye KA, Bursill CA, Lambert G, Tabet F, Barter PJ. The metabolism and anti-atherogenic properties of HDL. J Lipid Res. 2009;50 Suppl:S195-200.
86. Yanai H, Katsuyama H, Hamasaki H, Abe S, Tada N, Sako A. Effects of dietary fat intake on HDL metabolism. J Clin Med Res. 2015;7(3):145-9.
87. Giles-Corti B, Gunn L, Hooper P, Boulange C, Zapata-Diomedi B, Foster S. Built environment and physical activity: state of the art In: Nieuwenhuijsen M, editor. Urban Development, Environmental Exposures, and Health (in press)2018.
88. Arundel J, Lowe M, Hooper P, Roberts R, Rozek J, Higgs C, et al. Creating liveable cities in Australia: mapping urban policy implementation and evidence-based national liveability indicators. 2017. Report No.: 0987284193.
89. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of personality and social psychology. 1986;51(6):1173.
90. Pearce N, Vandenbroucke JP, Lawlor DA. Causal Inference in Environmental Epidemiology: Old and New Approaches. Epidemiology. 2019;30(3):311-6.
91. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia; 2008.

92. Ara I, Aparicio-Ugarriza R, Morales-Barco D, Nascimento de Souza W, Mata E, Gonzalez-Gross M. Physical activity assessment in the general population; validated self-report methods. Nutr Hosp. 2015;31 Suppl 3:211-8.
93. Handy S, Cao XY, Mokhtarian PL. Self-selection in the relationship between the built environment and walking - Empirical evidence from northern California. J Am Plan Assoc. 2006;72(1):55-74.
94. Gebel K, Bauman AE, Sugiyama T, Owen N. Mismatch between perceived and objectively assessed neighborhood walkability attributes: prospective relationships with walking and weight gain. Health Place. 2011;17(2):519-24.
95. Cerin E, Conway TL, Adams MA, Barnett A, Cain KL, Owen N, et al. Objectively-assessed neighbourhood destination accessibility and physical activity in adults from 10 countries: An analysis of moderators and perceptions as mediators. Soc Sci Med. 2018;211:282-93.
96. Wijndaele K, Healy GN, Dunstan DW, Barnett AG, Salmon J, Shaw JE, et al. Increased cardiometabolic risk is associated with increased tv viewing time. Med Sci Sports Exerc. 2010;42(8):1511-8.
97. Wong D. The modifiable areal unit problem (MAUP). The SAGE handbook of spatial analysis. 2009;105:23.
98. Kwan MP. The uncertain geographic context problem. Ann Am Assoc Geogr. 2012;102(5):958-68.
99. Chaix B, Merlo J, Evans D, Leal C, Havard S. Neighbourhoods in eco-epidemiologic research: delimiting personal exposure areas. A response to Riva, Gauvin, Apparicio and Brodeur. Soc Sci Med. 2009;69(9):1306-10.
100. Laatikainen TE, Hasanzadeh K, Kytta M. Capturing exposure in environmental health research: challenges and opportunities of different activity space models. Int J Health Geogr. 2018;17(1):29.
101. Koohsari MJ, Badland H, Giles-Corti B. (Re)Designing the built environment to support physical activity: Bringing public health back into urban design and planning. Cities. 2013;35:294-8.
102. Boakye-Dankwa E, Barnett A, Pachana NA, Turrell G, Cerin E. Associations between latent classes of perceived neighborhood destination accessibility and

walking behaviors in older adults of a low-density and a high-density city. Journal of aging and physical activity. 2019;27(2):553-64.

103. Giles-Corti B, Ryan K, Foster S. Increasing density in Australia: maximising the health benefits and minimising the harm. Melbourne, Australia: National Heart Foundation of Australia; 2012. Report No.: 1743450125.
104. VanderWeele TJ. Invited commentary: structural equation models and epidemiologic analysis. Am J Epidemiol. 2012;176(7):608-12.
105. Arcaya M, James P, Rhodes JE, Waters MC, Subramanian SV. Urban sprawl and body mass index among displaced Hurricane Katrina survivors. Prev Med. 2014;65:40-6.
106. Veitch J, Salmon J, Crawford D, Abbott G, Giles-Corti B, Carver A, et al. The REVAMP natural experiment study: the impact of a play-scape installation on park visitation and park-based physical activity. Int J Behav Nutr Phys Act. 2018;15(1):10.
107. Miller HJ, Tribby CP, Brown BB, Smith KR, Werner CM, Wolf J, et al. Public transit generates new physical activity: evidence from individual GPS and accelerometer data before and after light rail construction in a neighborhood of Salt Lake City, Utah, USA. Health Place. 2015;36:8-17.
108. Frank LD, Hong A, Ngo VD. Causal evaluation of urban greenway retrofit: a longitudinal study on physical activity and sedentary behavior. Prev Med. 2019;123:109-16.
109. Giles-Corti B, Knuiman M, Timperio A, Van Niel K, Pikora TJ, Bull FC, et al. Evaluation of the implementation of a state government community design policy aimed at increasing local walking: design issues and baseline results from RESIDE, Perth Western Australia. Prev Med. 2008;46(1):46-54.
110. Mensah GA, Cooper RS, Siega-Riz AM, Cooper LA, Smith JD, Brown CH, et al. Reducing cardiovascular disparities through community-engaged implementation research: a national heart, lung, and blood institute workshop report. Circ Res. 2018;122(2):213-30.
111. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2015;132(9):873-98.

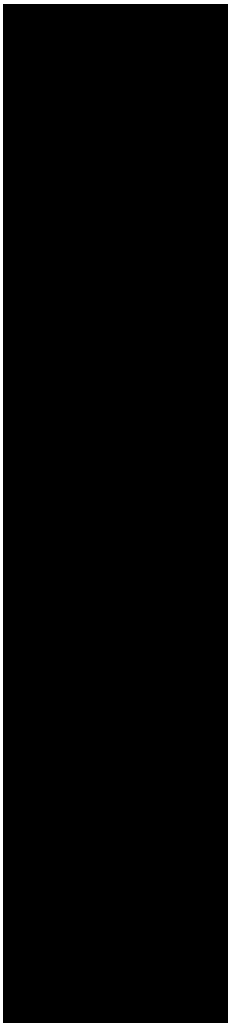
112. Koohsari MJ, Kaczynski AT, Hanibuchi T, Shibata A, Ishii K, Yasunaga A, et al. Physical activity environment and Japanese adults' body mass index. Int J Environ Res Public Health. 2018;15(4):11.
113. Alfonzo M, Guo Z, Lin L, Day K. Walking, obesity and urban design in Chinese neighborhoods. Prev Med. 2014;69 Suppl 1:S79-85.
114. Giles-Corti B, Sallis JF, Sugiyama T, Frank LD, Lowe M, Owen N. Translating active living research into policy and practice: one important pathway to chronic disease prevention. J Public Health Policy. 2015;36(2):231-43.
115. Healthy Liveable Cities Group. NHMRC Centre for Research Excellence in Healthy, Liveable Communities: Final Report. Melboure, Australia: Centre for Urban Research, RMIT University; 2018.
116. Durand CP, Andalib M, Dunton GF, Wolch J, Pentz MA. A systematic review of built environment factors related to physical activity and obesity risk: implications for smart growth urban planning. Obes Rev. 2011;12(5):e173-82.
117. National Heart Foundation. Blueprint for an Active Australia. Melbourne, Australia; 2019.
118. House of Representatives Standing Committee on Infrastructure, Transport and Cities. Building Up and Moving Out. Inquiry into the Australian Government's role in the development of cities. Canberra, Australia: Parliament of the Commonwealth of Australia; 2018.
119. Australian Bureau of Statistics. Regional population growth, Australia (cat. no. 3218.0). Canberra, Australia; 2018.

APPENDIX I: RESEARCH PORTFOLIO

AI.1: Statement of Contributions of to Jointly-Authored Manuscripts Included in the Thesis

1. Chandrabose, M., Rachele, J. N., Gunn, L., Kavanagh, A., Owen, N., Turrell, G., Giles-Corti, B., Sugiyama, T. (2019). Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. Obes Rev, 20(1), 41-54. doi:10.1111/obr.12759

(Included in **Section 2.2)**

	Name	Nature of contribution	Extent of contribution	Signature
1	Manoj Chandrabose	Conceived, developed a search strategy, performed database searches, screened and extracted data, developed the quality assessment tool, assessed the quality, conducted meta-analyses, and wrote the manuscript	65%	
2	Jerome N Rachele	Assisted in planning the study and developing a search strategy and quality assessment tool, screened and extracted data, and provided critical review for intellectual content	4%	
3	Lucy Gunn	Assisted in planning the study and developing a search strategy and quality assessment tool, screened and extracted data, and provided critical review for intellectual content	4%	
4	Anne Kavanagh	Assisted in planning the study and developing the quality assessment tool, and provided critical review for intellectual content	4%	
5	Neville Owen	Assisted in planning the study and developing the quality assessment tool, and provided critical review for intellectual content	4%	
6	Gavin Turrell	Assisted in planning the study and developing the quality assessment tool, and provided critical review for intellectual content	4%	
7	Billie Giles-Corti	Assisted in planning the study and developing the quality assessment tool, and provided critical review for intellectual content	4%	
8	Takemi Sugiyama	Conceived, guided in planning the study and developing a search strategy, mediated the discrepancies in screening, developed the quality assessment tool, and wrote the manuscript	11%	

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Jun 23, 2019

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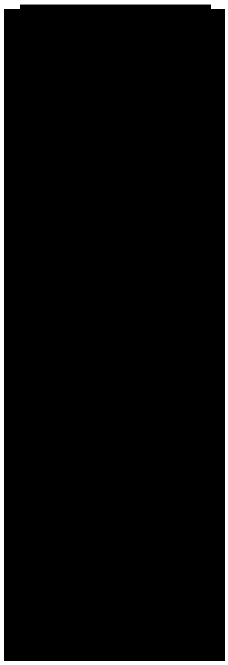
License date	Jun 23, 2019
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Obesity Reviews
Licensed Content Title	Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies
Licensed Content Author	M. Chandrabose, J. N. Rachele, L. Gunn, et al
Licensed Content Date	Sep 25, 2018
Licensed Content Pages	1
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print
Portion	Full article
Will you be translating?	No
Title of your thesis / dissertation	Long-term Impacts of Neighbourhood Built Environments on Cardio-metabolic Health
Expected completion date	Jul 2019
Expected size (number of pages)	150
Requestor Location	Mr. Manoj Chandrabose Level 5, 215 Spring Street Melbourne, Victoria 3000 Australia Attn: Mr. Manoj Chandrabose
Publisher Tax ID	[redacted]
Total	

2. Chandrabose M, Owen N, Giles-Corti B, Turrell G, Carver A, Sugiyama T. Urban Densification and 12-Year Changes in Cardiovascular Risk Markers. J Am Heart Assoc. 2019;8(15): e013199. doi:10.1161/JAHA.119.013199

(Included in **Section 4.1)**

	Name	Nature of contribution	Extent of contribution	Signature
1	Manoj Chandrabose	Conceptualised and designed the study, calculated built environment variables, developed an analytical strategy and conducted statistical analysis, and wrote the manuscript	65%	
2	Neville Owen	Conceived, assisted in conceptualisation, and provided critical review for intellectual content	8%	
3	Billie Giles-Corti	Assisted in conceptualisation, and provided critical review for intellectual content	4%	
4	Gavin Turrell	Assisted in conceptualisation, and provided critical review for intellectual content	4%	
5	Alison Carver	Assisted in conceptualisation, and provided critical review for intellectual content	4%	
6	Takemi Sugiyama	Guided in conceptualisation and designing, provided guidance for the spatial analysis, reviewed the analytical strategy, and wrote the manuscript	15%	

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3. Chandrabose M, Cerin E, Mavoa S, Dunston D, Carver A, Turrell G, Owen N, Giles-Corti B, Sugiyama T. Neighborhood walkability and 12-year changes in cardio-metabolic risk: the mediating role of physical activity. Int J Behav Nutr Phys Act. 2019;16(1):86. doi: 10.1186/s12966-019-0849-7

(Included in **Section 5.1)**

	Name	Nature of contribution	Extent of contribution	Signature
1	Manoj Chandrabose	Conceptualised and designed the study, calculated built environment variables, developed an analytical strategy and conducted statistical analysis, and wrote the manuscript	65%	[redacted]
2	Ester Cerin	Provided guidance for the statistical analysis, and provided critical review for intellectual content	5%	
3	Suzanne Mavoa	Provided guidance for the spatial analysis, and provided critical review for intellectual content	3%	
4	David Dunston	Assisted in designing the AusDiab study (a member of AusDiab Steering Committee), and provided critical review for intellectual content	3%	
5	Alison Carver	Assisted in conceptualisation, and provided critical review for intellectual content	3%	
6	Gavin Turrell	Assisted in conceptualisation, and provided critical review for intellectual content	3%	
7	Neville Owen	Assisted in conceptualisation, and provided critical review for intellectual content	3%	
8	Billie Giles-Corti	Assisted in conceptualisation, and provided critical review for intellectual content	3%	
9	Takemi Sugiyama	Guided in conceptualisation and designing the study, provided guidance for the spatial analysis, and wrote the manuscript	12%	

AI.2: Ethics Approval

Australian Catholic University human Research Ethics Commitee

From: Pratigya Pozniak on behalf of Res Ethics
To: Takemi Sugiyama
Cc: Res Ethics; Manoj Chandrabose; Gavin Turrell
Subject: 2018-1RN Registration of External Ethics Approval
Date: Tuesday, 22 May 2018 11:48:59 AM

Dear Takemi,

Principal Investigator: Prof Takemi Sugiyama
Co-Investigator: Prof Gavin Turrell, Prof Neville Owen, Prof Billie Giles-Corti
Student Researcher: Manoj Chandrabose (Doctoral)
Ethics Register Number: 2018-1RN
Project Title: Longitudinal Relationships between Built Environment Attributes and Changes in Markers of Cardio-metabolic Risk
Date Approved: 22/05/2018
Ethics Clearance End Date: 30/06/2019

The Australian Catholic University Human Research Ethics Committee has considered your application for registration of an externally approved ethics protocol and notes that this application has received ethics approval from Alfred Hospital [Reference: 39/11]. HREC also notes that RMIT University (Reference number: 20681-05/17) will provide access to data in a de-identified format.

The ACU HREC accepts the ethics approval with no additional requirements, save that ACU HREC is informed of any modifications of the research proposal and that copies of all progress reports and any other documents be forwarded to it. Any complaints involving ACU staff must also be notified to ACU HREC (National Statement 5.3.3)

We wish you well in this research project.

Regards,

Kylie Pashley
on behalf of ACU HREC Chair, Assoc Prof. Michael Baker

Senior Research Ethics Officer | Office of the Deputy Vice Chancellor (Research) Australian Catholic University
T: +61 2 9739 2646 E: res.ethics@acu.edu.au

Alfred Hospital Ethics Commitee

TheAlfred

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **39/11 AusDiab 3: emerging risk factors for and long-term incidence of cardio-metabolic diseases**

Principal Researcher: **Professor Jonathan Shaw**

Amendment:
Change to research personnel –
Addition of Mr Manoj Chandrabose

have been approved in accordance with your amendment application dated **6-Jul-2016** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Professor John J. McNeil
Chair, Ethics Committee

Date: **13-Jul-2016**

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

AI.3: Trainings Attended during the Candidature

- "*Multilevel Statistical methods*" short course, conducted by Prof S V Subramanian. (Harvard University), organized by the McCaughey VicHealth Community Wellbeing Unit, University of Melbourne [March 2016]
- "*Geographic Information Systems (GIS) Specialization*" online training, conducted by University of California, Davis on Coursera online training platform [March-May 2016]
- "*Intermediate Bayesian Statistics*" workshop, hosted by Statistical Society of Australia [July 2016]
- "*Structural Equation Modelling*" workshop, organized by Institute for Health and Ageing (IHA), Australian Catholic University (ACU) [November 2016]
- "*Python*" course, hosted by ACU eResearch [January 2017]
- "*Ozri 2017*" GIS user conference, organized by ESRI Australia [August 2017]
- "*Accelerometer Data Collection*" training, conducted by the International Physical Activity and Environment Network (IPEN) research team from UC San Diego, organized by IHA, ACU [August 2017]
- "*Project Management: Databases and Quality Control*" workshop, conducted by the IPEN research team from UC San Diego, organized by IHA, ACU [August 2017]

APPENDIX II: SUPPLEMENTARY MATERIALS FOR CHAPTER 2

The following supplementary tables, corresponding to the systematic review (Study One) published in the *Obesity Reviews* journal, are accessible through https://doi.org/10.1111/obr.12759

- **Table S1:** Search terms used
- **Table S2:** Methodological Quality-Assessment Tool
- **Table S3:** Summary of data extracted from reviewed articles
- **Table S4:** Methodological quality and sample size assessment scores
- **Table S5:** Complete meta-analysis results

APPENDIX III: SUPPLEMENTARY MATERIALS FOR CHAPTER 3

AIII.1: A Flow Chart of Spatial Analysis Process

The following flow chart outlines the spatial analysis process undertook by the candidate as a part of this Thesis to develop built environment data for the AusDiab study participants.

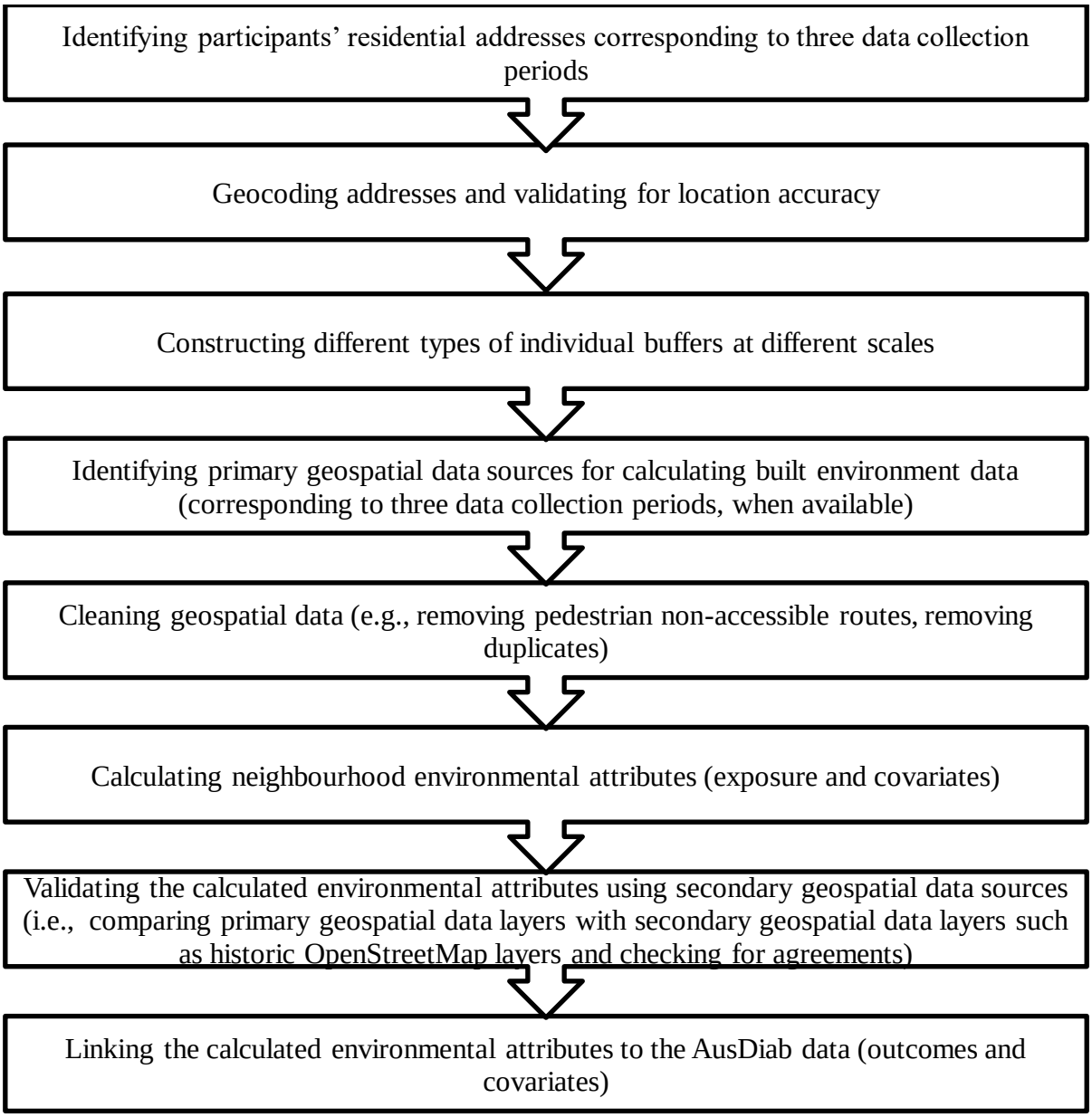


Figure AIII.1: A Flow Chart of Spatial Analysis Process

AIII.2: Security Protocol for Linking Environmental Data to the AusDiab Data

The AusDiab data, including participant address data, were available at the Baker Heart and Diabetes Institute (Baker). A subproject was undertaken by the Centre for Research Excellence (CRE) in Healthy, Liveable Communities to develop Geographic Information Systems (GIS)-based built environment data for AusDiab study participants. The CRE was led by Professor Billie Giles-Corti (associate supervisor), Centre for Urban Research, Royal Melbourne Institute of Technology (RMIT). The CRE's GIS project (including the candidate's GIS related works) was conducted at RMIT. Since participant address data is sensitive and confidential, Baker and RMIT implemented a security protocol to protect the identity of AusDiab study participants. The security protocol is described in Figure A2.1. Each box is labelled with the institute where the corresponding task was performed.

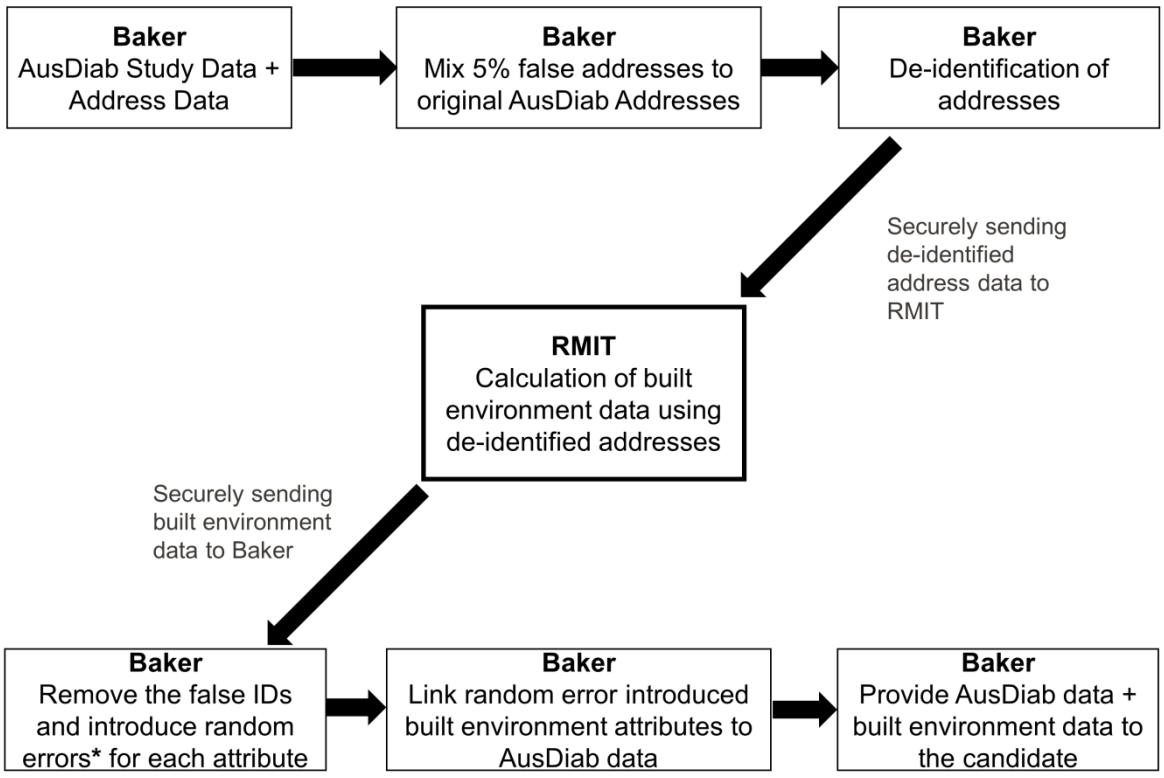


Figure AIII.2: The Security Protocol for Handling Address Data when Calculating Built Environment Attributes

*Note: * random errors were small enough to have no discernible influence on statistical analyses*

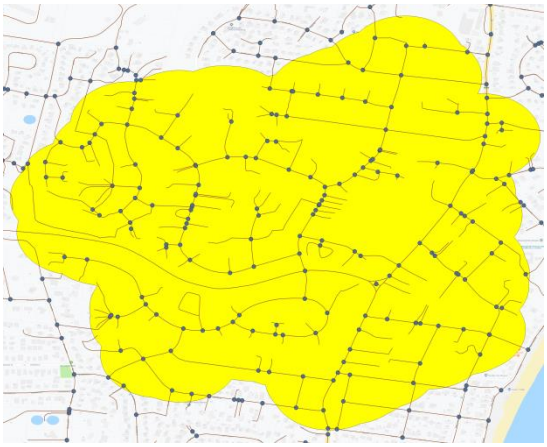
AIII.3: A Comparison of Intersection Density Measures

For calculating a walkability index, the following two intersection density measures were compared:

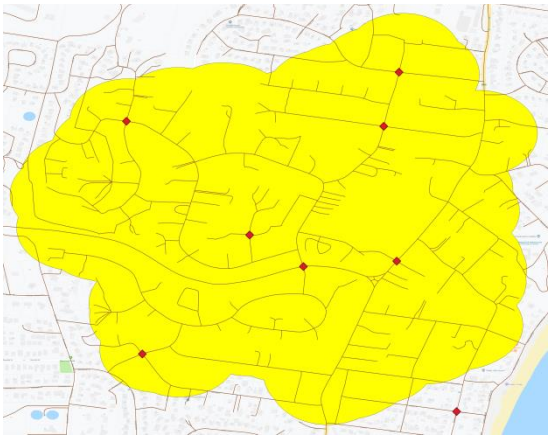
- 3-way measure: number of 3-or-more-way intersections/ buffer area
- 4-way measure: number of 4-or-more-way intersections/ buffer area

The following maps compare these two measures in two buffers in AusDiab study areas.

Buffer A

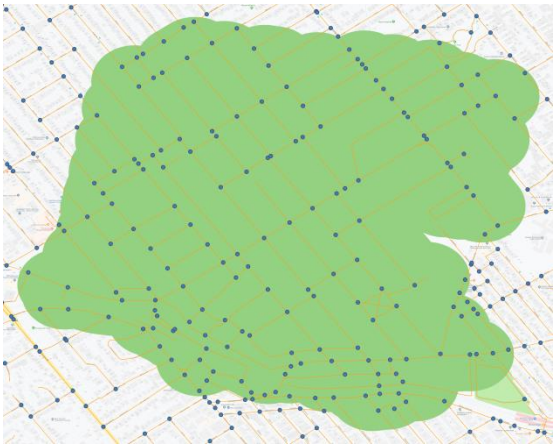


3-way measure = 130 intersections/ km^2



4-way measure = 5 intersections/ km^2

Buffer B



3-way measure = 77 intersections/ km^2

4-way measure = 15 intersections/ km^2

Figure III.3: A Comparison of Two Intersection Density Measures

Buffer A has low street connectivity than Buffer B (visual examination). But, the 3-way measure of Buffer A was greater than the 3-way measure of Buffer B. In contrary, the 4-way measure of Buffer B was greater than the 4-way measure of Buffer A. Thus, it's decided to use the 4-way measure as an appropriate measure of street connectivity.

AIII.4: Measurement of Additional Built Environment Variables

Parks

PSMA Australia's Transport & Topography dataset includes a GREENSPACE theme, which contains polygons representing locations and shapes of local urban parks, through to state and national parks. PSMA's GREENSPACE data from both the 2005 and 2012 releases were compared with historical Open Street Map park data (the validation data), and it was found that the 2005 release was relatively more comprehensive (in comparison to the 2012 release), and comparable with the validation data. Thus, PSMA's GREENSPACE 2005 release data was used to calculate the following park related measures:

- Number of parks within the participant's individual buffer
- Street distance to the nearest park access point from the participant's residence
- Area of the nearest park to the participant's residence
- The sum of the areas of the parks that can be reached by the participant's individual buffer

Street-network distance to the city centre

For each of the seven states and Northern Territory, the location of the General Post Office (GPO) of each capital city was considered as the corresponding city centre location. PSMA Australia's Transport & Topography road network dataset (the 2012 release) was used to calculate road distance measures. Pedestrian non-accessible roads were not removed as in the case of creating street-network buffers.

PedShed ratio

PedShed ratio (ratio of the area within street-network buffer to the area within straight-line buffer) was calculated as an additional measure of street connectivity. A higher ratio indicates more connectivity.

Walk Score®

Walk Score® is a web-based measure of walkability, which can be obtained from www.walkscore.com. This score uses publicly available web-based geospatial data sources (e.g., Google Maps, Open Street Maps) to derive a walkability index (ranges from

0 to 100) to a location based on the road distance to nearby commercial and public frequently-visited destinations (1). The R package walkscoreAPI v 1.2 (2) was used query the Walk Score database for participants' residential locations (distance offsetted locations were used for querying). It was observed that, for most participants' locations, these scores have been calculated using geospatial data sources that have been updated in 2016 or later.

Remoteness area index

The Remoteness Area (RA) index is a measure used by the Australian Bureau of Statistics (ABS) to define remoteness of locations (3). This measure is calculated using an algorithm (Accessibility Remoteness Index of Australia, ARIA) developed by the University of Adelaide's National Centre for Social Applications of Geographic Information Science (GISCA). The following five categories are used to determine remoteness of locations:

- Major Cities of Australia
- Inner Regional Australia
- Outer Regional Australia
- Remote Australia; and
- Very Remote Australia

The ABS releases RA index digital boundaries in GIS data formats, which were used to assign those indices to participants' locations.

References:

1. Duncan DT, Aldstadt J, Whalen J, Melly SJ, Gortmaker SL. Validation of Walk Score® for estimating neighborhood walkability: an analysis of four US metropolitan areas. International journal of environmental research and public health. 2011 Nov;8(11):4160-79.
2. Whalen J. walkscoreAPI: Walk Score and Transit Score API v 1.2. https://cran.r-project.org/web/packages/walkscoreAPI/index.html
3. ABS. *Statistical geography -Australian standard geographical classification (ASGC), digital boundaries, 2006 (cat. no. 1259.0.30.002)*. Canberra: Australian Bureau of Statistics; 2006.

AIII.5: Active Australia Survey Items Used to Measure Physical Activity

AusDiab: The Australian Diabetes, Obesity and Lifestyle Study

General Questionnaire

Physical activity

In this section, I will ask you some questions about the time that you may have spent doing physical activities as part of your everyday lives.

The following questions are about any physical activities that you may have done in the last week.

Walking

In the last week, how many times have you walked continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?

☐☐ times

What do you estimate was the total time that you spent walking in this way in the last week?

(In hours and/or minutes - fill in all circles on answer sheet)

☐☐ hours ☐☐ minutes

Vigorous physical activity

The next question does not include household chores, gardening or yard work.

In the last week, how many times did you do any vigorous physical activity which made you breathe harder or puff and pant? (e.g. tennis, jogging, cycling, keep fit exercises).

☐☐ times

What do you estimate was the total time that you spent doing this vigorous physical activity in the last week?

(In hours and/or minutes - fill in all circles on answer sheet)

☐☐ hours ☐☐ minutes

Moderate physical activity

The next question does not include household chores, gardening or yard work.

In the last week, how many times did you do any other more moderate physical activities that you have not already mentioned? (e.g. lawn bowls, golf, gentle swimming, etc.)

☐☐ times

What do you estimate was the total time that you spent doing these activities in the last week?

(In hours and/or minutes - fill in all circles on answer sheet)

☐☐ hours ☐☐ minutes

APPENDIX IV: SUPPLEMENTARY MATERIALS FOR CHAPTER 4

The following supplementary materials, corresponding to the Study Two published in the *Journal of the American Heart Association*, are accessible through https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013199

- **Material S1:** Explaining Multilevel Growth Models
- **Table S1:** Baseline characteristics of stayers, movers, and drop-outs, AusDiab study
- **Table S2:** Associations of annual absolute population densification with changes in cardiovascular risk markers, AusDiab study
- **Table S3:** Associations of annual population densification with changes in cardiovascular risk markers among metropolitan residents, AusDiab study
- **Figure S1:** Three-level data structure of the study
- **Figure S2:** Scatterplots for relationships of annual relative population densification and annual absolute population densification with baseline population density.

APPENDIX V: SUPPLEMENTARY MATERIALS FOR CHAPTER 5

The following supplementary materials, corresponding to the Study Three published in the *International Journal of Behavioral Nutrition and Physical Activity*, are accessible through https://doi.org/10.1186/s12966-019-0849-7.

- **Table S1**: Baseline characteristics of stayers, movers, and drop-outs, AusDiab study (1999-2012)
- **Material S1**: Active Australia Survey items used to measure physical activity
- **Material S2:** Calculating changes using values measured at three observation points
- **Material S3**: Details of the three-level linear growth model used in the study