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Estimating the effect of lifestyle over the course of adulthood on all-cause and cause-specific mortality

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ABSTRACT

Background

Existing evidence linking lifestyle-related factors (body mass index [BMI], physical activity, sedentary behaviour, and alcohol consumption) to mortality is primarily based on observational studies with single-time-point exposure assessments. However, the effects of lifestyle changes or benefits of long-term adherence to public health recommendations during adult life cannot be estimated without using data from additional time points. Despite the fact that many cohort studies have assessed exposures and confounders repeatedly over time, a limited number of studies have used these data. This thesis aims to estimate the effects of time-varying lifestyle-related exposures during adulthood on mortality using longitudinal studies with repeated exposure assessments. Lifestyle-related factors to be examined include BMI, physical activity, sedentary behaviour, and alcohol consumption.

Methods

This PhD research included four studies. In Study 1, I performed a systematic review of mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour. I summarised the study findings and critically appraised the analytic approaches used to analyse data on time-varying exposures. Studies 2 to 4 used data from three Australian cohorts with multiple data collection waves to estimate the mortality effects of adulthood lifestyle-related exposures. The three cohorts were the Melbourne Collaborative Cohort Study (MCCS), the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), and the Australian Longitudinal Study on Women's Health (ALSWH) 1946-1951 birth cohort. Deaths in the three cohorts were ascertained through probabilistic record linkage to the Australian National Death Index. In Study 2, I used a group-based trajectory model to identify clusters of individuals in the MCCS who followed similar body mass index trajectories over adulthood, and estimated mortality for the identified trajectories. In Studies 3 and 4, I used the parametric g-formula to analyse the data from the AusDiab study and the ALSWH 1946-1951 birth cohort, which estimated potential mortality outcomes under hypothetical sustained population interventions on physical activity, TV viewing, and alcohol consumption.

Results

The systematic review found that the most common way to treat repeatedly measured exposures was to categorise them into a summary variable. The most widely used statistical analysis method was Cox regression. The included studies were subject to moderate to serious risk of bias, mainly arising from inadequate adjustment of time-varying confounding, selection of participants affected by post-baseline vital status, questionnaire-based exposure assessment, and changes from measured exposure during long passive follow-up periods. Despite heterogeneity in methods, the findings suggest that maintaining a more physically active and less sedentary lifestyle over adulthood reduces all-cause and cardiovascular mortality moderately.

Findings from the MCCS suggested that midlife obesity increased mortality even when BMI was normal in early adulthood, and prolonged exposure to borderline obesity could increase mortality, compared with maintaining a higher-normal BMI. In AusDiab, sustained interventions during adulthood to increase leisure-time physical activity could lower all-cause mortality, and there might be limited gain from intervening on television (TV) viewing time in a relatively healthy population. In the ALSWH 1946-51 birth cohort, compared with having no alcohol intervention, sustained interventions of moderate alcohol consumption (up to 30 grams of ethanol per day) may lower all-cause mortality but not cancer mortality, while a high intake intervention (more than 30 grams of ethanol per day) would increase both all-cause and cancer mortality over the long term for women in their midlife.

Conclusion

The systematic review summarised existing mortality studies using physical activity and sedentary behaviour measured at multiple time points. It also critically appraised the methods used and potential sources of bias in these studies. The group-based trajectory approach used in the MCCS contributed to the understanding of mortality outcomes experienced by individuals who followed different BMI developmental courses over adulthood. The two applications of parametric g-formula in the AusDiab and ALSWH 1946-1951 birth cohort demonstrated estimation of causal effects of hypothetical sustained population interventions, producing policy relevant evidence.

Collectively, research in this thesis showed that, with data measured at multiple time points, one could estimate mortality effects of long-term exposures, which cannot be achieved using

single-time-point measurements. The research also demonstrated the use of observational data to emulate a target trial that is infeasible or unethical in a real-world setting. When analysed with appropriate statistical methods, exposure and confounder data assessed at multiple time points can be used to estimate potential mortality outcomes under hypothetical long-term lifestyle interventions.

Future research should leverage repeatedly collected data in existing cohort studies to address the methodological challenges inherent in typical epidemiological studies. This would help provide greater insight into mortality effects of initiating or maintaining a certain health behaviour, guide population interventions, and refine evidence for guidelines and recommendations.

Declaration

This is to certify that

1. The thesis comprises only my original work towards the PhD except where indicated in the preface,
2. Due acknowledgement has been made in the text to all other material used,
3. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies, and appendices.

Yi Yang, January 2022

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This thesis would not have been possible without the support of many people.

First and foremost, I would like to express my sincere gratitude to my supervisors, Professor Dallas English, Associate Professor Allison Hodge, Associate Professor Brigid Lynch, and Dr Pierre-Antoine Dugué. Dallas is a great supervisor with fine personal qualities.¹ He is knowledgeable, humble, and a researcher of integrity. His belief in me and unwavering support played a huge role in helping me navigate through the PhD journey. I am particularly grateful that Dallas ensured I had all the support and guidance I needed during difficult times, especially in hard COVID-19 lockdowns. Allison is a great supervisor, sharp-minded, insightful, and honest. I have always admired her ability to synthesise and interpret information critically, and write succinctly with clarity. I am thankful to her for always providing timely and valuable feedback on my work. Brigid has always been a wonderful supervisor since my master's project. I am thankful for her significant contribution in advising my research, especially on my work related to physical activity. I am also grateful to her for encouraging me to connect and collaborate, build my network, and share my research. Pierre has been an excellent supervisor, a talented researcher, and an extremely smart and funny person. Pierre introduced me to research in epidemiology when he and Brigid supervised my master's project. I appreciated all the discussions we had at Cancer Council Victoria, and I am thankful for his critical feedback on my work which often helped me get on the right track.

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¹ Lynch BM and Neale RE. 2017. Australasian Epidemiological Association Mentoring Award. Personal qualities and mentoring capabilities of Professor Dallas English: A guide to the development of future mentors in epidemiology.

I was fortunate to be surrounded by a team of inspiring and supportive PhD peers and colleagues in the Melbourne School of Population and Global Health at the University of Melbourne and the Cancer Epidemiology Division at Cancer Council Victoria. I valued their support in every stage of my PhD, as well as all the fun we had together.

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Yi Yang 杨熠

26 January 2022 腊月廿四 小年夜

Preface

I am a grateful recipient of a Melbourne Research Scholarship and a Cancer Council Victoria studentship. My thesis uses data from three Australian cohort studies: the Melbourne Collaborative Cohort Study, the Australian Diabetes, Obesity and Lifestyle study, and the Australian Longitudinal Study on Women's Health (also known as Women's Health Australia) 1946-1951 birth cohort. My thesis chapters include three published first author peer-reviewed research papers and one manuscript in progress of finalising for submission to a peer-reviewed journal. I conceived the research questions, drafted analysis plans, performed data analyses, and wrote the manuscript drafts. At thesis submission, I provided co-author authorisation forms indicating that my contribution to each manuscript was at least 60%.

Co-author contributions to publication chapters

Chapter 3 of this thesis includes material from the following paper published at *International Journal of Epidemiology*:

Yi Yang, Suzanne C Dixon-Suen, Pierre-Antoine Dugué, Allison M Hodge, Brigid M Lynch, Dallas R English. Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings. *International Journal of Epidemiology* 2021; dyab181, doi:10.1093/ije/dyab181

All co-authors were involved in developing the systematic review protocol. Suzanne C Dixon-Suen, Pierre-Antoine Dugué, Brigid M Lynch and Dallas R English participated in titles and abstract screening as second reviewers. Suzanne C Dixon-Suen and Dallas R English reviewed full texts for study eligibility, extracted the data and performed risk of bias assessment for the included studies as second reviewers. All co-authors revised the manuscript draft critically and approved the final manuscript.

Chapter 5 includes material from the following paper published at *BMJ Open*:

Yi Yang, Pierre-Antoine Dugué, Brigid M Lynch, Allison M Hodge, Amalia Karahalios, Robert J MacInnis, Roger L Milne, Graham G Giles, Dallas R English. Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study. *BMJ Open* 2019;9:e030078.doi: 10.1136/bmjopen-2019-030078

My co-authors Pierre-Antoine Dugué, Brigid M Lynch, Allison M Hodge and Dallas R English were involved in planning the study. I performed the statistical analyses and drafted the manuscript with support from Pierre-Antoine Dugué, Brigid M Lynch, Allison M Hodge and Dallas R English. Graham G Giles conceived the overall cohort study (Melbourne Collaborative Cohort Study). All co-authors helped shape the research, provided critical feedback, and approved the final manuscript.

Chapter 6 includes material from the following paper published in *Medicine and Science in Sports and Exercise*:

Yi Yang, Allison M. Hodge, Pierre-Antoine Dugué, Elizabeth J. Williamson, Paul A. Gardiner, Elizabeth L.M. Barr, Neville Owen, David W. Dunstan, Brigid M Lynch, Dallas R English. Mortality effects of hypothetical interventions on physical activity and TV viewing. *Medicine & Science in Sports & Exercise* 2021;53(2):316-323. DOI: 10.1249/mss.0000000000002479.

My co-authors Allison M Hodge, Pierre-Antoine Dugué, Brigid M Lynch, and Dallas R English were involved in planning the study. I performed the statistical analysis with statistical advice from Elizabeth J Williamson. I drafted the manuscript with support from Allison M Hodge, Pierre-Antoine Dugué, Brigid M Lynch, and Dallas R English. Paul A Gardiner, Elizabeth LM Barr, Neville Owen, and David W Dunstan contributed to the data interpretation and provided critical feedback for the manuscript draft. All authors approved the final manuscript.

Chapter 7 includes material from the following manuscript that are being finalised for submission to a peer-reviewed journal:

Yi Yang, Allison M. Hodge, Brigid M. Lynch, Pierre-Antoine Dugué, Elizabeth J. Williamson, Harindra Jayasekara, Gita Mishra, Dallas R. English. Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women.

My co-authors Allison M Hodge, Pierre-Antoine Dugué, Brigid M Lynch, and Dallas R English were involved in planning the study. I developed the analysis plan with statistical advice from Elizabeth J Williamson and performed the analysis at University of Queensland where the data were hosted. All co-authors contributed to the result interpretation, provided critical feedback for the manuscript draft, and approved the current manuscript draft to be included in this thesis.

Publications and conference presentations

First-author publications and presentations arising from my PhD

Peer-reviewed papers:

1. **Yang Y**, Dugué PA, Lynch BM, Hodge AM, Karahalios A, MacInnis RJ, Milne RL, Giles GG, English DR. Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study. *BMJ Open* 2019; 9: e030078.
2. **Yang Y**, Hodge AM, Dugué PA, Williamson EJ, Gardiner PA, Barr ELM, Owen N, Dunstan DW, Lynch BM, English DR. Mortality effects of hypothetical interventions on physical activity and TV viewing. *Medicine & Science in Sports & Exercise* 2021;53: 316-23.
3. **Yang Y**, Dixon-Suen SC, Dugué PA, Hodge AM, Lynch BM, English DR. Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings. *International Journal of Epidemiology* 2021. DOI: 10.1093/ije/dyab181.
4. **Yang Y**, Hodge AM, Lynch BM, Dugué PA, Williamson EJ, Jayasekara H, Mishra G, English DR. Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women. [in progress for submission]

Presentations:

1. Oral presentation on “Mortality under long-term interventions on physical activity and TV viewing” at the Australasian Epidemiological Association (AEA) Conference, October 2019, Brisbane, Australia.
2. Poster presentation on “Hypothetical interventions on physical activity and TV viewing in relation to all-cause mortality”, at the Society for Epidemiologic Research (SER) Conference, June 2019, Minneapolis, USA.

3. Guest presentation on implementation of the parametric g-formula at the Contemporary Epidemiology Short Course, Melbourne School of Population and Global Health, Melbourne, Australia. 2019.
4. Guest presentation on “Hypothetical lifestyle interventions to reduce mortality: an application of the parametric g-formula” at Washington University School of Medicine in St. Louis (Public Health Sciences Division), June 2019, St. Louis, USA.
5. Oral presentation on “Adulthood body mass index trajectories and mortality” at the Australasian Epidemiological Association (AEA) Conference, October 2018, Fremantle, Australia

Other first author publications during the course of my PhD:

Peer-reviewed paper:

1. **Yang Y**, Lynch BM, Dugué PA, Karahalios A, MacInnis RJ, Bassett JK, McAleese A, Sinclair C, Giles GG, Milne RL, Hodge AM, English DR. Latent Class Trajectory Modeling of Adult Body Mass Index and Risk of Obesity-Related Cancer: Findings from the Melbourne Collaborative Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2021;30: 373-9.

Letter to editors

1. **Yang Y**, Lynch BM, van Roekel EH. Letter by Yang et al Regarding Article, “Accelerometer-Measured Physical Activity and Sedentary Behavior in Relation to All-Cause Mortality: The Women’s Health Study”. *Circulation*. 2018 Jul 3;138(1):114-5.

Co-authored publications during the course of my PhD

Peer-reviewed papers:

1. Jayasekara H, MacInnis RJ, Barroso LL, Mayen-Chacon AL, Cross AJ, Wallner B, Palli D, Ricceri F, Pala V, Panico S, Tumino R, Kühn T, Kaaks R, Tsilidis K, Sánchez

- MJ, Amiano P, Ardanaz E, López MDC, Merino S, Rothwell JA, Boutron-Ruault MC, Severi G, Sternby H, Sonestedt E, Bueno-de-Mesquita B, Boeing H, Travis R, Sandanger TM, Trichopoulou A, Karakatsani A, Peppas E, Tjønneland A, **Yang Y**, Hodge AM, Mitchell H, Haydon A, Room R, Hopper JL, Weiderpass E, Gunter MJ, Riboli E, Giles GG, Milne RL, Agudo A, English DR, Ferrari P. Lifetime alcohol intake, drinking patterns over time, and risk of stomach cancer: a pooled analysis of data from two prospective cohort studies. *Int J Cancer*. 2021 Feb 7. doi: 10.1002/ijc.33504. Epub ahead of print. PMID: 33554339.
2. Lynch BM, Dixon-Suen SC, Varela AR, **Yang Y**, English DR, Ding D, Gardiner PA, Boyle T. Approaches to improve causal inference in physical activity epidemiology. *Journal of Physical Activity and Health*. 2020 Jan 1;17(1):80-4.
 3. Bassett J, MacInnis RJ, **Yang Y**, Hodge AM, Lynch BM, English DR, Giles GG, Milne RL, Jayasekara H. "Alcohol intake trajectories during the life course and risk of alcohol-related cancer: a prospective cohort study" [under review at *International Journal of Cancer*]
 4. Zohreh Basiri; **Yi Yang**; Fiona J Bruinsma; Anna K Nowak; Kerrie L McDonald; Katharine J Drummond; Mark A Rosenthal; Eng-Siew Koh; Rosemary Harrup; Elizabeth Hovey; David Joseph; Geza Benke; Robyn Leonard; Robert J MacInnis; Roger L Milne; Graham G Giles; Claire M Vajdic; Brigid Lynch. Physical activity and glioma: a case-control study with follow-up for survival. [under review at *Cancer Causes and Control*]
 5. Christopher Swain; Julie K. Bassett; Allison M. Hodge; David W Dunstan; Neville Owen; **Yi Yang**; Harindra Jayasekara; James R. Hébert; Nitin Shivappa; Robert J MacInnis; Roger L. Milne; Dallas R. English; Brigid M. Lynch. Television viewing time and all-cause mortality: interactions with BMI, physical activity, smoking, and dietary factors. [under review at *International Journal of Behavioral Nutrition and Physical Activity*]

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List of Abbreviations

ADLs	Activities of daily living
AIC	Akaike information criterion
ALSWH	Australian Longitudinal Study on Women's Health
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BIC	Bayesian information criterion
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DAG	Directed acyclic graph
df	Degree of freedom
EPIC	European Prospective Investigation into Cancer and Nutrition
FEV1	Forced expiratory volume in one second
FFQ	Food frequency questionnaire
GAMM	Generalised additive mixed model
GBTM	Group-based trajectory model
GEE	Generalised estimating equation
h/d	Hours/day
h/w	Hours/week
HDL	High density lipoprotein
HIIT	High intensity interval training
HR	Hazard ratio
HRS	Health and Retirement Study
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IPTW	Inverse probability treatment weighting
IQR	Interquartile range
IRSAD	The Index of Relative Socio-economic Advantage and Disadvantage
IRSD	The Index of Relative Socio-economic Disadvantage
LDL	Low density lipoprotein
ll	Log likelihood

LTPA	Leisure time physical activity
MCCS	Melbourne Collaborative Cohort Study
MDS	Mediterranean diet score
MET	Metabolic-equivalent
MI	Myocardial infarction
MICE	Multiple imputation using chained equations
MICT	Moderate intensity continuous training
MSM	Marginal structural model
N	Number
NDI	National Death Index
NHIS	National Health Interview Survey
NHMRC	Australian National Medical Research Council
NHS	Nurses' Health Study
NI	No information
NPFS	Health Professionals Follow-up Study
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PA	Physical activity
PHS	Physicians' Health Study
PLCO	The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
RD	Risk difference
ROBINS-E	Risk of Bias In Non-randomised Studies – of Exposures
ROBINS-I	Risk of Bias In Non-randomised Studies – of Interventions
RR	Relative risk (in Chapter 3); Risk ratio (in all other chapters)
SBP	Systolic blood pressure
SD	Standard deviation
SEIFA	Socio-Economic Indexes for Areas
SF36	36-item short form survey
TR	Trajectories
TV	Television
WHO	World Health Organization

Chapter 1 Introduction

1.1 Rationale

Ongoing research suggests that a large proportion of disease and early deaths may be prevented by following a healthier lifestyle.¹ For example, smoking cessation is an important lifestyle modification in terms of preventing premature deaths from cancer.^{2,3} The harmful effects of tobacco smoking have been documented since 1950.⁴⁻⁶ Establishment of tobacco's causal relationship with lung cancer and mortality is recognised as one of the most important milestones in the history of epidemiology. Following the establishment of the relationship between smoking and mortality from lung cancer, evidence emerged that age of cessation determined the extent of risk reduction in former smokers compared with the risk for continuing smokers,^{2,7,8} suggesting that duration of exposure and timing of behaviour change play an important role. The resultant public health message is that, although it is never too late to benefit from quitting smoking, gains in life expectancy are highest for those who quit at a younger age.⁹ However, evidence regarding the modification of other lifestyle-related factors in relation to mortality is less clear. Associations derived from observational studies are mostly based on single exposure measurements that might reflect only the effect of recent exposure at the time of assessment. Whether and how long-term exposure to, or changes in, lifestyle-related factors over time will affect mortality are not well understood.

Randomised controlled trials of long-term interventions on lifestyle-related behaviour are often infeasible and could be unethical. In the absence of randomised controlled trials, inferences about the effect of lifestyle-related exposures on mortality are made from observational studies, mostly from cohort studies. In a conventional prospective cohort study, a group of participants are recruited at study entry (i.e., baseline), when data on their exposure to a wide range of factors are collected. Participants are then followed passively through disease registries and vital statistics listings. Several lifestyle-related factors have shown associations with mortality in studies that analysed baseline exposure data, including body mass index (BMI),¹⁰⁻¹² physical activity,¹³ sedentary behaviour,¹⁴ and alcohol consumption.¹⁵ Some cohort studies have also updated data on exposure status on one or more occasions during follow-up,¹⁶ which allows researchers to study the effects of changes in exposure.

1.2 Problem statement

To date, the evidence relating lifestyle exposures to mortality is largely based on exposures measured at single time points. There has been relatively limited research examining exposure over the long term, despite many cohort studies having collected exposures at multiple time points. Investigating the effect of time-varying lifestyle exposures on mortality has the potential to improve our understanding of their influence on risk of early deaths, and to refine the evidence that contributes to the development of guidelines and recommendations.

The conventional approach to analysing data from longitudinal settings may produce biased results if confounders (i.e., common causes of lifestyle-related exposures and mortality) are also time-varying and are affected by prior exposure. Application of alternative approaches when data allow will contribute to reducing the risk of bias and improving the quality of evidence for informing policy and public health decisions.

1.3 Aims and objectives

This thesis aims to estimate the effects of time-varying lifestyle-related exposures during adulthood on mortality using longitudinal studies with repeated exposure assessments. Lifestyle-related factors to be examined include BMI, physical activity, sedentary behaviour, and alcohol consumption.

When I began my research, there were published systematic reviews that summarised mortality studies with more than one assessment of BMI (or body mass, commonly referred to as body weight) and alcohol consumption as exposures, but no published systematic reviews that had summarised mortality studies that used assessments of physical activity and sedentary behaviour from multiple time points (details presented in Chapter 2). Therefore, the first objective of the thesis is as follows:

Objective 1: To systematically review the analytic methods and findings from mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour.

The objectives corresponding to the main thesis aim are as follows:

Objective 2: To examine BMI trajectories over adulthood and their effect on mortality.

Objective 3: To estimate the effects of sustained physical activity and sedentary behaviour over adulthood on mortality.

Objective 4: Estimate the effect of sustained midlife alcohol consumption on mortality in women.

1.4 Thesis outline

This thesis comprises eight chapters. Detailed background information regarding the current epidemiological evidence on associations between lifestyle-related risk factors (i.e., BMI, alcohol consumption, physical activity, and sedentary behaviour) and mortality, and motivation for research in the thesis will be provided in Chapter 2. The first section of Chapter 2 will present an overview of current literature on adulthood BMI and mortality. The second section will be a review of evidence on adulthood alcohol consumption and mortality. The two sections will be mainly based on published systematic reviews. The third section presents a short summary of evidence on adulthood physical activity, sedentary behaviour and mortality. Since no systematic review had been conducted for evidence generated from studies using physical activity and sedentary behaviour measured at multiple time points, Chapter 3 will present the findings from a systematic review I conducted to summarise and discuss the findings and the analytic methods used in such studies (to address Objective 1).

In Chapter 4, I will provide an overview of the three cohort studies whose data were used to address Objectives 2 to 4. The three studies are the Melbourne Collaborative Cohort Study (MCCS), the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) and the Australian Longitudinal Study on Women's Health (ALSWH) 1946-1951 birth cohort. In this chapter, I will also outline the methodological challenges in analysing time-varying data and describe the statistical methods used for the analyses in this thesis.

Chapters 5 to 7 present three studies where I explored the relationship between lifestyle-related factors over time and mortality, and each was written as a manuscript for publication. In Chapter 5, I will present the findings from the MCCS where I explored adulthood BMI trajectories and their impacts on mortality. In Chapter 6, I will present the findings from the AusDiab study where I compared the mortality risks under different hypothetical sustained interventions on physical activity and television (TV) viewing time (a measure of common leisure-time sedentary behaviour). Chapter 7 will present findings on the effect of sustained

midlife alcohol consumption on mortality. This was achieved through emulating a target trial of various alcohol drinking interventions using observational data from the ALSWH 1946-1951 birth cohort and comparing mortality risks under these hypothetical interventions.

In the final chapter (Chapter 8), I will summarise the main findings of this thesis, and review the strengths and limitations of the research. In this chapter, I will also discuss implications of the findings including the contributions to the evidence base informing public health policy and practice, Finally, I will discuss directions for future research.

Chapter 2 Background

2.1 Body mass index and mortality

The World Health Organization (WHO) defines overweight and obesity as the ‘abnormal or excessive fat accumulation that presents a risk to health’. Excessive fat accumulation, often referred to as excessive adiposity, can be assessed using various anthropometric measures, for example, waist circumference, waist-to-hip ratio, and BMI.¹⁷ The most commonly used tool to measure overall adiposity is BMI, a simple index of body mass relative to height. It is calculated as body mass in kilograms divided by the square of height in meters (kg/m^2). The WHO uses BMI to classify excess adiposity as overweight and obesity. A BMI over 25 kg/m^2 is considered overweight, and over 30 kg/m^2 is obese (Table 2-1). The WHO classifications of BMI are the same for adults of all ages, and for males and females.^{18,19} Since BMI is easy to measure and calculate on a large scale, it has been the most widely used tool to assess the effect of overweight and obesity on risks of various health outcomes, including mortality. Although BMI should be considered as only a rough indicator of overweight and obesity, as it may not reflect the same adiposity in different individuals, it is in general a useful population-level measure.

Table 2-1. WHO classifications of BMI

BMI range	Classification
Below 18.5 kg/m^2	Underweight
18.5 to 24.9 kg/m^2	Normal weight
25.0 to 29.9 kg/m^2	Overweight or pre-obesity
30.0 to 34.9 kg/m^2	Class I obesity
35.0 to 39.9 kg/m^2	Class II obesity
40 kg/m^2 or greater	Class III obesity

The prevalence of obesity has doubled since 1980 globally and continues to increase.²⁰ More than 600 million adults and 100 million children were obese in 2015.²⁰ Elevated BMI has been associated with numerous adverse health outcomes that contribute to a higher risk of premature death,²¹ from causes such as cardiovascular disease,²² diabetes,²³ musculoskeletal disorders,²⁴ poor mental health,²⁵ and certain types of cancers. A recent evaluation by the International Agency for Research on Cancer (IARC) Handbooks of Cancer Prevention programme concluded that cancers of the following sites were obesity-related: oesophagus adenocarcinoma, postmenopausal breast, liver, gallbladder, renal cell, colon and rectum, multiple myeloma, meningioma, thyroid, gastric cardia, pancreas, ovary, and corpus uteri.²⁶

It is infeasible and unethical to conduct randomised controlled trials to study the effect of overweight or obesity on mortality. Therefore, most existing evidence supporting the relationship between overweight and obesity (assessed using BMI) is based on observational studies. Many large prospective cohort studies have examined BMI (typically measured once at baseline) and mortality outcomes. Some large prospective cohort studies reported that overweight BMI has a lower all-cause mortality than BMI in the normal range. A meta-analysis of 97 cohort studies (including 2.88 million participants and 27,000 deaths) in 2013 reported that only severe baseline obesity ($\text{BMI} \geq 35 \text{ kg/m}^2$) was associated with higher all-cause mortality compared with normal BMI (hazard ratio [HR]=1.29, 95% confidence interval [CI], 1.18 to 1.41).²⁷ No association was found for class I obesity, and all-cause mortality was lower for overweight relative to normal weight (HR=0.94, 95% CI 0.91 to 0.96). However, this meta-analysis did not account for confounding from smoking (smokers have lower BMI but higher mortality than non-smokers) and comorbidities (people with major illnesses often lose weight and have higher mortality than healthy people).

Because smoking and comorbidities have strong effects on both BMI and mortality, researchers started to conduct analysis of the BMI-mortality relationship in participants who had never smoked and had no major illnesses at baseline.^{10,28} In 2016, a systematic review and meta-analysis of 230 cohort studies with more than 30 million participants and 3.7 million deaths found that underweight, overweight, and obesity as defined by BMI were all associated with increased mortality after removing confounding from smoking.¹¹ In all participants (198 studies), current smokers (18 studies), and former smokers (15 studies), the BMI with lowest mortality was 25 kg/m^2 . In never smokers, the optimal BMI range for lowest mortality was 23 to 24 kg/m^2 . In never smokers who also did not have comorbidities, the mortality was lowest in the range 22 to 23 kg/m^2 .¹¹ Similarly, a large global collaborative study analysed individual-level data from 239 cohort studies from Asia, Australia and New Zealand, Europe, and North America and accounted for confounding from smoking and comorbidities. The analysis showed that, in never smokers without known chronic disease, all-cause mortality was lowest in normal BMI (between 20 kg/m^2 and 25 kg/m^2) and increased in overweight (HR=1.11, 95% CI 1.10 to 1.11) and obese BMI range (class I: HR=1.44, 95% CI 1.41 to 1.47; class II: HR=1.92, 95% CI 1.86 to 1.98; and class III: HR=2.71, 95% CI 2.55 to 2.86) relative to normal BMI.¹²

More recently, Mendelian randomisation has been used to investigate the causal relation between BMI and mortality. Mendelian randomisation is a development in genetic

epidemiology that uses genetic variants as a proxy for modifiable risk factors to circumvent potential biases in observational studies. Because associations between genetic variants and the outcome are not confounded by other behavioural or environmental factors, Mendelian randomisation has similar properties to an intention-to-treat analysis in a randomised controlled trial under the assumptions that (1) the variants are associated with the exposure, (2) the variants are not associated with common causes of the exposure and the outcome, and (3) the variants must not be associated with the outcome other than through their link with the exposure.^{29,30} Recent Mendelian randomisation studies used BMI-associated genotypic variation to test the causal relationship between BMI and all-cause and cause-specific mortality.^{31,32} The lowest mortality was observed at genetically determined BMI of 25 kg/m² and evidence supports the causal role of higher BMI in increasing mortality.^{31,32}

In summary, a large body of evidence for the BMI-mortality relationship has been accumulated in studies using BMI assessed at one time point, where findings suggested that higher-normal BMI has the lowest mortality. In cohort studies, BMI was often measured at baseline. Participants were then followed until death or end of administrative follow-up. However, an individual's BMI is likely to change over time. It is likely that the BMI measured at one time point in adult life does not reflect time-varying BMI values that could all contribute to the risk of death. Therefore, repeated BMI assessments over time are preferred when studying the effect of long-term exposure patterns. Similarly, in Mendelian randomisation studies, the genetic variants used were associated with BMI measured at one time point.^{33,34} It was highlighted that if an exposure is time-varying, and the values across multiple time points can all affect the outcome, Mendelian randomisation analysis can be biased if the measurement at only one of the time points is used.³⁵

2.1.1 Evidence on BMI assessed at multiple time points over adulthood and risk of mortality

Current evidence based on BMI measured only once overlooks the time-varying nature of this exposure. For example, someone who has recently become obese could have a different risk of death compared with someone who has been obese throughout adulthood. The latter would have longer exposure to adiposity-related pathophysiological alterations such as hypertension, dyslipidaemia, fibrinolysis, insulin resistance, inflammation, and immune system alterations.³⁶⁻

³⁸ Longer exposure to obesity is associated with adverse health outcomes that could contribute

to a higher risk of death such as unfavourable biomarker profiles as indicated by higher C-peptide and lower IGFBP-1 concentrations,³⁹ type 2 diabetes,^{40,41} cancer,⁴²⁻⁴⁴ and cardiovascular disease.⁴⁵

Some studies used BMI measured at two time points to study exposure change and its effect on mortality. A systematic review and meta-analysis in 2017 summarised the evidence from 24 studies (including 434,694 participants with 31,978 deaths) that examined changes in BMI or weight (classified using data from two time points) in healthy adult populations from midlife onwards, and subsequent all-cause, cardiovascular disease and cancer mortality.⁴⁶ The meta-analysis found that when compared with stable weight or BMI, weight loss or BMI drop was associated with higher risk of all-cause (HR=1.45, 95% CI 1.34 to 1.58) and cardiovascular disease mortality (HR=1.50, 95% CI 1.32 to 1.70); increased weight or BMI was associated with higher risk of cardiovascular disease mortality (1.21, 95% CI 1.07 to 1.36) and a small increase in all-cause mortality (HR=1.07, 95% CI 1.01 to 1.13). Associations with cancer mortality were weak for both weight or BMI reduction (HR=1.19, 95% CI 0.97 to 1.46) and weight or BMI gain (HR=1.04, 95% CI 0.96 to 1.13).

To summarise, the meta-analysis found that weight loss or BMI reduction increased mortality markedly and gaining weight or increasing BMI increased mortality moderately. However, as the authors of the meta-analysis noted, most studies did not collect information on reasons for weight loss.⁴⁶ The elevated mortality in people who lost weight could be confounded by smoking or major comorbidities (e.g., cancer), as they lead to unintentional weight loss and increased mortality. The results cannot be interpreted as evidence that weight loss (especially as a result of intentional weight management) is harmful for mortality outcomes.

2.1.2 Literature review: BMI trajectories and risk of mortality

Using data at only two time points to classify changes in exposure (i.e., stable, gain, or loss) can fail to identify more unique patterns of BMI over time.⁴⁷ Recent studies have considered BMI trajectories including more time points to identify more complex patterns of changes. I performed a literature search on Ovid Medline from inception to 1 February 2019 to identify studies investigating associations between BMI trajectories and all-cause and cause-specific mortality in generally healthy populations. Because of the relatively small number of studies on BMI, I extended the search terms to include studies that used other anthropometric measures. The search terms are included in Box 2-1. Titles and abstracts for studies were then

screened for relevance to this review. A study was included if it used more than two time points to classify BMI trajectories in a generally healthy population and reported relative risks for at least one mortality outcome. Reference lists of included studies were manually searched for eligible studies.

Box 2-1. Search terms used on Ovid Medline search: BMI trajectories and mortality

1. (body mass index or body size or body shape or adiposity or obesity or overweight or BMI or waist).ti.
2. (death or mortality).ti.
3. trajector*.ti,ab.
4. 1 and 2 and 3
5. limit 4 to ed=19460101-20190201

A total of 10 studies were identified from the search; one study was excluded because it was conducted in dialysis patients,⁴⁸ and three studies were excluded because only two time points were used to define weight change.⁴⁹⁻⁵¹ One study was identified through manual search of reference lists.⁵² However, it was superseded by a more recent paper using data from the same cohort,⁵³ therefore not included. Characteristics of the remaining six eligible studies⁵³⁻⁵⁸ are presented in Table 2-2. Four studies were conducted in the United States of America (USA),^{53,55-57} one in Canada,⁵⁸ and one in Japan.⁵⁴ The six studies modelled BMI trajectories in various stages during adulthood: two studies^{53,56} used mid- to late-adulthood data, two^{54,58} examined BMI trajectories in older adults, one⁵⁷ included data from early to late adulthood, and one⁵⁵ used data from childhood to mid-adulthood.

One of the six eligible studies used a generalised additive mixed model (GAMM) to model BMI trajectories in the Physicians' Health Study (PHS).⁵⁶ GAMM is a flexible modelling strategy using nonparametric regression to account for within-individual correlation by using random effects.⁵⁹ BMI trajectories were modelled for two groups of male physicians (n=14,172 in total): those who died before the age of 75, and those who did not die before the age of 75. The group dying at a younger age followed a trajectory with a higher mean BMI throughout adulthood (25, 25, 26, and 26 kg/m² at ages 40, 50, 60, 70 years), while the group dying at 75 years or older had mean BMIs of 24, 25, 25, 25 kg/m² at the same ages. In a validation cohort of 5,732 new physicians, participants following the trajectory of the men dying at age < 75 had higher risk of all-cause mortality (odds ratio [OR]=1.35, 95% CI 1.01 to 1.78) and cardiovascular disease mortality (OR=1.92, 1.10 to 3.35), compared with those followed the

lower and flatter trajectory. These findings suggest that maintaining a normal BMI throughout adulthood reduces the risk of overall and cardiovascular disease mortality.⁵⁶

The remaining five studies used a semiparametric group-based trajectory modelling (GBTM) approach to identify distinct BMI or body shape trajectories in the study sample over multiple time points during the participants' lifetime.^{53-55,57,58} The model is an application of finite mixture modelling and assumes that the population is composed of a mixture of groups following homogenous BMI trajectories.⁶⁰ These studies identified various BMI or body shape trajectories (listed in Table 2-3). In general, BMI increased from early to mid-adulthood, and declined at older ages in some groups. In older adults, Murayama et al.⁵⁴ found that only 5% of the participants followed a stable overweight trajectory and other participants followed trajectories that started with normal BMI and declined over time in Japanese seniors aged at least 60 years. Wang et al.⁵⁸ found similar declining trajectories in Canadian seniors, with overall higher initial BMI (including normal, overweight, and obese initial BMI) than the Japanese population.

Mortality outcomes associated with the trajectory groups are presented in Table 2-3. Zheng⁵³ found that participants with trajectories of sustained overweight from age 51 to 77 years (participants aged 51 to 61 at baseline) had the lowest all-cause mortality in the US Health and Retirement Study. Similarly, Murayama et al.⁵⁴ found that, relative to a declining trajectory with an initial BMI in the mid-normal range, the stable overweight trajectory group experienced lower all-cause mortality in a Japanese population aged at least 60 years at baseline.⁵⁴ Wang et al.⁵⁸ found that, in older Canadian population (aged 65 to 79 at baseline), a declining trajectory that started with an overweight BMI had the lowest all-cause mortality in men, and a declining trajectory that started with class I obesity had the lowest mortality in women.

In contrast, a study that modelled body shape trajectories using data from earlier life (age 5 to 50 years) found that people who were always lean had the lowest all-cause, cardiovascular disease, and cancer mortality; people with a substantial increase in body size (from lean to heavy) had a higher risk, whereas people who were heavy since childhood had the highest risk.⁵⁵ Another study in US men also showed higher mortality due to prostate cancer in both 'normal to obese' and 'overweight to obese' adulthood BMI trajectories, compared with a stable normal BMI trajectory.⁵⁷

In general, the trajectories identified in each study was specific to its study population and the life stage examined. Overall, BMI (and body shape for one study⁵⁵) increased around early and mid-adulthood (either gradually or more steeply for some groups), and declined during older ages. Mortality outcomes reported in the studies were not directly comparable to one another as the hazard ratios were for unique trajectories in different samples, and for various life stages.

It is worth mentioning that, in studies using repeated exposure data, information is lacking on whether weight/BMI reduction or a downward BMI trend was intentional (e.g., as a result of weight management) or unintentional (e.g., due to newly diagnosed illnesses). The lack of data on the intentionality of weight reduction limits the interpretability of mortality outcomes in these two distinct groups.

2.1.3 Summary

There is extensive evidence suggesting overweight and obese BMI increases mortality in adults compared with normal BMI, based on studies that used BMI measured at one time point in adulthood. However, given the time-varying nature of BMI, these studies could not estimate the mortality effect of BMI pattern over adulthood. Some studies used exposure from two time points to study changes in anthropometric measures, including BMI and weight, and found midlife BMI or weight change (both gain and loss) increased mortality compared with stable BMI or weight. Although data from two time points are better at reflecting exposure change than studies using only baseline data, they are often insufficient to capture a complete picture of BMI over adulthood. A small number of studies modelled trajectories of BMI or body shape using data collected from multiple time points over adulthood. Using more data points, trajectories showed a more complete picture of exposure patterns over adulthood in specific populations and could potentially reduce misclassifications of exposure from using only two data points. For example, a difference in BMI between two time points several years apart might be attributable to random variation, but the underlying pattern might be relatively stable when looking through more time points. This motivated the study of adulthood BMI trajectories and their impacts on mortality using data from the Melbourne Collaborative Cohort Study (MCCS).

Table 2-2. Summary of study characteristics: BMI trajectories and mortality

First author, year	Study characteristics	Exposure	Trajectory period	Outcome (Deaths/participants)	Method	Follow-up	Adjusted covariates
Zheng, 2013 ⁵³	USA; Health and Retirement Study; 53% women; 51-61 years	BMI	Age 51 to 77 years	All-cause (2,526/9,538)	GBTM; Cox regression	1992–2008 (up to 16 years)	Sex, ethnicity, marital status, income, education, smoking, physical activities, activities of daily living limitations, angina, heart attack or heart failure, arthritis, emphysema or bronchitis, diabetes, stroke, cancer, bone fracture, and self-rated general health.
Murayama, 2015 ⁵⁴	Japan; National Survey of the Japanese Elderly; 55% women; ≥ 60 years	BMI	From 1987 (mean age 70) to 2006	All-cause (2,628/4,869)	GBTM; Cox regression	1987-2012 (mean 14 years)	Age, sex, marital status, currently working, education, income, weight, smoking, alcohol, physical activity, history of cardiovascular disease, stroke, lung disease, liver disease, and kidney disease; self-rated health and functional status at baseline; and entry wave.
Song, 2016 ⁵⁵	USA; The Nurses' Health Study (NHS); 100% women; 30-55 years	Body shape	Age 5 to 50 years	All-cause (20415/80266), CVD (3953/80266), Cancer (6744/80266)	GBTM; Cox regression	Age 60 to 2012 (median 15 years)	Age, height, race, smoking, family history of cancer, history of lower gastrointestinal endoscopy, multivitamin use, NSAID use, history of physical examination, mammography, menopausal hormone therapy, physical activity, alcohol, and diet quality.
	United States; Health Professionals Follow-up Study (HPFS); 0% women; 40-75 years	Body shape	Age 5 to 50 years	All-cause (14943/36622), CVD (4813/36622), Cancer (4098/36622)	GBTM; Cox regression	Age 60 to 2012 (median 16 years)	Age, height, race, smoking, family history of cancer, history of lower gastrointestinal endoscopy, multivitamin use, NSAID use, history of physical examination, prostate specific antigen test, physical activity, alcohol, and diet quality.

Table 2-2. Summary of study characteristics: BMI trajectories and mortality (continued)

First author, year	Study characteristics	Exposure	Trajectory period	Outcome (Deaths/participants)	Method	Follow-up	Adjusted covariates
Ding, 2016 ⁵⁶	United States; Physicians' Health Study (PHS); 0% women; 40-84 years	BMI	Age 40 to 70 years	All-cause (111/5732), CVD (NR/5732), cancer (NR/5732)	GAMM, logistic regression	Up to 15 years (1997 to 2012)	Age, hypertension, hypercholesterolemia, diabetes, cardiovascular incidence, race, smoking, physical activity, red meat intake, fruit and vegetable intakes, and total energy intake.
Kelly, 2017 ⁵⁷	United States; Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial; 0% women; 55-74 years	BMI	Ages 20 to 70 years	Prostate cancer mortality (255/69873)	GBTM; Cox regression	Median 11.5 years	Age, trial arm, screening centre, race, education, marital status, diabetes, smoking, myocardial infarction, prostate-specific antigen history in the past 3 years, and family history of prostate cancer.
Wang, 2017 ⁵⁸	Canada; The Household component of the Canadian National Population of Health Survey (NPHS); 62% women; 65-79 years	BMI	Age 65 to 97 years	642/1480	GBTM; Cox regression	18 years	Age, race, education, place of residence, disability, physical active, smoking, alcohol, change in number of chronic conditions.

BMI: body mass index; CVD: cardiovascular disease; GBTM: group-based trajectory models; GAMM: generalized additive mixed model; NSAID: non-steroidal anti-inflammatory drug; NR: not reported.

Table 2-3. Relative risks for mortality for each trajectory group in the included studies.

First author, year	Exposure	Trajectories	Relative risk ^ (95% confidence interval)		
			All-cause mortality	CVD mortality	Cancer mortality
Zheng, 2013	BMI	Overweight stable	1		
		Normal weight, decrease	1.64 (1.43 to 1.88)		
		Normal weight, increase	1.09 (0.98 to 1.22)		
		Overweight obesity	0.99 (0.88 to 1.11)		
		Class I obese, increase	1.11 (0.97 to 1.28)		
		Class II/III, obese increase	1.83 (1.52 to 2.21)		
Murayama, 2015	BMI	Low-normal weight, decrease	1.17 (1.02 to 1.33)		
		Mid-normal weight, decrease	1		
		High-normal weight, decrease	0.82 (0.72 to 0.93)		
		Overweight, stable	0.72 (0.54 to 0.96)		
Song, 2016, Nurses' Health Study (NHS)	Body shape	Lean, stable	1		
		Lean, moderate increase	1.05 (1.01 to 1.09)	1.10 (1.01 to 1.19)	1.04 (0.98 to 1.10)
		Lean, marked increase	1.29 (1.23 to 1.35)	1.65 (1.49 to 1.82)	1.13 (1.04 to 1.23)
		Medium, table/ increase	1.05 (1.01 to 1.09)	1.08 (0.99 to 1.19)	1.03 (0.97 to 1.11)
		Heavy, stable/ increase	1.48 (1.39 to 1.57)	2.00 (1.77 to 2.25)	1.24 (1.11 to 1.38)
Song, 2016, Health Professionals Follow-up Study (HPFS)	Body shape	Lean, stable	1	1	1
		Lean, moderate increase	1.03 (0.98 to 1.08)	1.11 (1.02 to 1.21)	0.96 (0.88 to 1.06)
		Lean, marked increase	1.14 (1.08 to 1.20)	1.32 (1.21 to 1.44)	1.01 (0.92 to 1.11)
		Medium, stable/ increase	1.06 (1.01 to 1.11)	1.19 (1.09 to 1.29)	0.99 (0.91 to 1.08)
		Heavy, stable/ increase	1.16 (1.10 to 1.23)	1.32 (1.19 to 1.47)	1.07 (0.96 to 1.19)
Ding, 2016	BMI	Trajectory with age at death >=75 years	1	1	1
		Trajectory with age at death <75 years	1.35 (1.01 to 1.78)	1.92 (1.10 to 3.35)	1.08 (0.72 to 1.63)

Table 2-3. Relative risks for mortality for each trajectory group in the included studies (continued).

First author, year	Exposure	Trajectories	Relative risk ^ (95% confidence interval)		
			All-cause mortality	CVD mortality	Cancer mortality
Kelly, 2017	BMI	Stable normal			1
		Normal to overweight			0.99 (0.74 to 1.32)
		Normal to obese			1.95 (1.21 to 3.12)
		Stable overweight			1.51 (0.96 to 2.36)
		Overweight to obese			2.65 (1.35 to 5.18)
Wang, 2017 (Women)*	BMI	Overweight-Normal weight	1		
		Normal Weight-Down	1.21(0.84 to 1.74)		
		Obese I-Down	0.56(0.35 to 0.90)		
		Obese II- Down	1.34(0.50 to 3.58)		
Wang, 2017 (Men)	BMI	Overweight-Normal weight	1		
		Normal Weight-Down	1.66(1.20 to 2.29)		
		Overweight-Stable	1.25(0.92 to 1.67)		
		Obese-Stable	1.98(1.28 to 3.16)		

BMI: body mass index; CVD: cardiovascular disease. ^Ding et al reported odds ratios. Other studies reported hazard ratios. *Women with less than three health conditions.

2.2 Alcohol and mortality

Section 2.2 summarises existing evidence on the relationship between alcohol consumption and mortality. Several systematic reviews have been published on this topic. This section mainly draws from the findings of these systematic reviews.

Alcohol (or ethanol), the active ingredient in alcoholic beverages, is one of the most consumed psychoactive substances in many cultures throughout history.⁶¹ People consume alcoholic beverages for a range of reasons and in different cultural and social contexts. People may drink for recreational purposes, to enhance creativity, overcome boredom, improve mood, or simply for intoxication.⁶² In Australia, drinking alcoholic beverages is a significant part of the culture and plays an important role in people's social lives. Qualitative research shows that, except for binge drinking (i.e., consuming alcohol at risky levels on a single occasion), consuming alcoholic beverages is a widely accepted behaviour while complete abstention from alcohol is uncommon.⁶³ However, excessive consumption of alcoholic beverages may cause multiple social and health problems for individuals and society. It can increase immediate risk of harm such as injury, self-harm, and violence. Binge drinking, in particular, contributes to higher risk of these immediate harms.⁶⁴⁻⁶⁶ Excessive alcohol consumption has also been related to a range of long-term health conditions in adults such as cardiovascular disease, several cancer types, long-term cognitive impairment, and liver diseases.⁶⁷⁻⁷⁰ These conditions could increase mortality over the long term.

While substantial evidence from observational studies that assessed alcohol consumption at single time points has shown that excessive drinking is associated with increased risk of adverse health outcomes, including mortality, some studies have suggested that drinking at low levels may reduce the risk of some cardiovascular disease outcomes.⁷¹ In addition, a meta-analysis of 44 short-term interventional studies of the effects of alcohol consumption on 13 biological markers related to coronary heart disease showed favourable changes in some biomarkers such as lower levels of fibrinogen and higher levels of adiponectin and high-density lipoprotein cholesterol, suggesting a protective effect of moderate alcohol consumption on coronary heart disease.⁷² Some prospective cohort studies also reported that light to moderate alcohol consumption is associated with lower mortality compared with abstention (often referred to as a 'J-shape' relationship).^{73,74} However, criticisms remain that the J-shape relationship is likely due to biases. It is possible that light to moderate drinkers have other characteristics that may explain their lower mortality compared with abstainers (i.e.,

confounding is present). The reduced mortality in low-volume drinkers compared with abstainers in some studies may also partly be explained by the inclusion of both former drinkers and lifetime abstainers in the reference category of “current abstainers”.^{15,75,76} The underlying reason may be that people are more likely to substantially reduce intake or quit alcohol to manage aging and deteriorating health, leading to poorer health profiles and higher mortality in current abstainers.^{15,75,77}

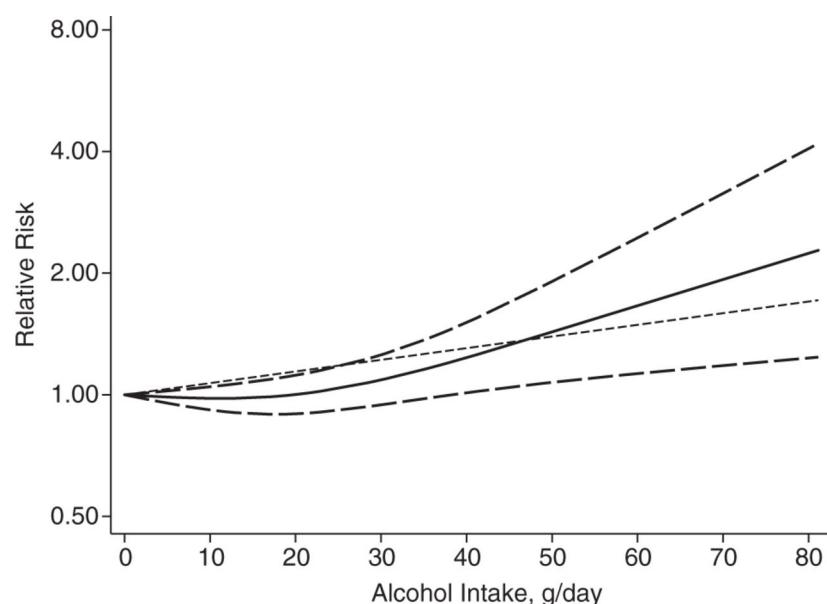
In 2020, the Australian National Medical Research Council (NHMRC) published the most recent Australian guidelines to reduce health risks from drinking alcoholic beverages. The guidelines for reducing the risk of alcohol-related disease or injury in healthy adults recommend no more than 100 grams of pure ethanol a week (i.e., 10 Australian standard drinks), and no more than 40 grams of pure ethanol (i.e., four Australian standard drinks) on any single day.⁷⁸ For the guideline development, the NHMRC commissioned an overview of systematic reviews on alcohol-related health benefits and harms.⁷⁹ Since there were no randomised controlled trials that examined long-term alcohol-related harm, evidence informing the guidelines was mainly drawn from observational studies. In relation to all-cause mortality, the overview identified seven systematic reviews.^{15,80-85} The systematic review with the most up-to-date search was considered, in which the primary exposure of interest was mean daily alcohol consumption assessed at baseline of cohort studies.¹⁵ The analysis included 87 cohort studies (367,103 deaths in 3,998,626 individuals). The authors found that when all studies were included in the meta-analysis, there was a J-shape relationship between alcohol consumption and all-cause mortality: compared with abstainers, mortality was lower in low-volume drinkers (1.3 to 24.9 grams of ethanol per day; relative risk= 0.86, 95% CI 0.83 to 0.90; mortality was higher in former drinkers (relative risk=1.22, 95% CI 1.14 to 1.31). When the meta-analysis was performed in 13 studies without abstainer bias (i.e., no former or occasional drinkers were included in reference group of abstainers), the J-shape relationship was less prominent (relative risk = 0.90, 95% CI 0.76 to 1.06 for low volume drinkers). When the meta-analysis was performed in six higher quality studies (e.g., strictly defined lifetime abstainers as reference group, good measure of alcohol intake, and controlling for smoking status), mortality was not lower in low-volume drinkers (relative risk=1.04, 95% CI 0.95 to 1.15).¹⁵ This is consistent with findings of an earlier review by Fillmore et al (2007).⁷⁵ The authors found that when studies excluded former and occasional drinkers from the abstainer reference group, there was limited evidence of lower mortality for moderate alcohol consumption.⁷⁵

2.2.1 Evidence on alcohol consumption assessed at multiple time points and mortality

It has been suggested that, instead of using baseline assessment, alcohol intake repeatedly measured should be the preferred measure, because consumption is likely to change over time.^{86,87} Misclassification of long-term consumption based on assessment at one time point could bias the estimate for the effect of alcohol on long-term health outcomes. The Australian National Drug Strategy Household Survey (2019) found that the prevalence of people consuming more than 20 grams of ethanol per day and the prevalence of binge drinking reduced after the previous version of NHMRC alcohol consumption guidelines were introduced in 2009.⁸⁸ In addition, more Australians reported that they had quit or reduced their alcohol intake (31% in 2019, an increase from 28% in 2016), mainly driven by health concerns.⁸⁸ This highlights the importance of considering alcohol consumption as a time-varying exposure to capture the changes that may affect health and mortality differently.

A systematic review and meta-analysis of alcohol consumption over adulthood and risk of death⁸⁰ identified nine studies published between 1966 and August 2012 (comprising 62,950 participants and 10,490 deaths) that used alcohol intake data measured repeatedly during follow-up assessments,⁸⁹⁻⁹⁶ or history of consumption recalled for different periods of life.⁹⁷ The exposure time assessed in the nine studies ranged from three years to lifetime history from age 12 years. Six studies classified exposure as changes in intake (e.g., stable, quit, increase, decrease); three summarised exposures based on intake averaged over time. The meta-analysis for average alcohol consumption over time in men (g/day, derived in six studies) showed a weak J-shape relationship with all-cause mortality, with the lowest mortality at lower intake levels and higher mortality for higher intakes (Figure 2-1). The pooled relative risks (relative to abstinence) were 0.90 (95% CI: 0.81 to 0.99) for 1 to 29 g/day, 1.19 (95% CI 0.89 to 1.58) for 30 to 59 g/day, and 1.52 (95% CI: 0.78 to 2.98) for 60 g/day or higher. Only four of the nine studies^{90,92,93,97} reported relative risks for women, thus the authors did not perform a meta-analysis for women. The meta-analysis could not eliminate the effect of illness-driven quitting because individual studies did not separate former drinkers from lifetime abstainers in the “abstinence” reference group.

Figure 2-1. Adjusted relative risk of death associated with average alcohol consumption over time in a meta-analysis of published studies for men, 1966–2012.



The vertical axis is on a log scale. Bold line, spline model; long-dashed lines, upper and lower confidence limits of spline model; short-dashed line, linear model. Originally Figure 2 from Jayasekera (2014),⁸⁰ reprinted with permission from American Journal of Epidemiology, Oxford University Press. Permission obtained on 02 January 2022.

Observational studies using data collected at multiple times face some methodological challenges. Firstly, as reported in the systematic review by Jayasekera *et al.*, some studies averaged intake patterns over time to create a summary measure, which might mask important behaviour changes between assessments.⁸⁰ For example, drinkers who maintained a moderate intake over time could be classified in the same group as heavy drinkers who have quit, while the two groups are likely to have different long-term mortality outcomes. Secondly, studies that included participants with alcohol data for multiple time points required the participants to survive and participate in more than one data collection wave. Selection bias was possible as both the exposure and the outcome might have affected selection of participants into the analysis (e.g., heavy drinkers were less likely to attend all data collections, and participants who died before post-baseline collection waves could not have participated). Thirdly, illness-driven change in alcohol consumption needs to be addressed. A study showed that people who quit alcohol consumption between data collection waves were more likely to have reported declined health.⁷⁷ When alcohol consumption assessed at multiple time points is the exposure of interest, time-varying health status is not only a confounder (i.e., a common cause of change in alcohol intake levels and mortality), but also an intermediate variable on a causal pathway (i.e., a result of earlier alcohol intake that contributes to mortality). This gives rise to time-

varying confounding that needs to be controlled appropriately. More details on adjustment of time-varying confounding will be provided in Chapter 4, where appropriate statistical methods are discussed. Finally, it is important to distinguish former drinkers from lifetime abstainers during data collection and analysis to disentangle the mortality outcomes in the two groups.

2.2.2 Summary

Current guidelines to reduce risk from alcohol drinking draw evidence about mortality from observational studies that measured alcohol intake at one time point. These studies found that high intakes of alcohol increased mortality. Some studies showed lower all-cause mortality for light or moderate consumption relative to abstention. This might be partly due to inclusion of former or occasional drinkers in the abstainer reference group. A meta-analysis of mortality studies that measured alcohol consumption at multiple time points showed a weak J-shaped relationship in men. However, lifetime abstainers could not be separated from former drinkers in the meta-analysis. Evidence based on repeatedly assessed alcohol intake in women was limited.

Current alcohol guidelines and public health policies will benefit from more studies that measure consumption repeatedly over time and address methodological challenges arising from time-varying exposure and confounding. More research including women are especially needed, as evidence is scarce despite the fact that women may be affected more by some of the alcohol-related diseases such as liver disease, breast cancer, and heart disease.^{69,98,99} These formed the motivation of the study of sustained alcohol consumption and mortality in women using repeatedly collected data from the ALSWH 1946-1951 birth cohort.

2.3 Physical activity, sedentary behaviour, and mortality

Both physical inactivity (lack of moderate-to-vigorous intensity physical activity) and sedentary behaviour (prolonged sitting or reclining with low energy expenditure) contribute to the risk of diseases (including leading causes of deaths like cancer and cardiovascular disease) and mortality.^{13,14,100-106} Although sedentary behaviour is at the lower end of a physical activity continuum, physical inactivity and sedentary behaviour are often viewed as separate behaviours with distinct sociodemographic and behavioural contexts and correlates.¹⁰⁶ A strong and consistent body of evidence exists, showing that physical inactivity is associated with higher mortality.^{13,102} More recently, sedentary behaviour has emerged as an additional risk factor.^{101,103,104,107} Since individuals can be simultaneously highly physically active (e.g., 60 minutes of vigorous physical activity after work) and highly sedentary (e.g., eight hours of sitting at work), it is important to consider the mortality effects of both behaviours. In 2016, The Lancet published its second series on physical activity which included the first harmonized meta-analysis directly comparing mortality between people with different levels of physical activity and sedentary behaviour.¹⁰⁸ The authors found that a high level of physical activity could possibly attenuate or even eliminate the detrimental effect of sedentary behaviour; but the level needed to achieve this (approximately 60-75 minutes of moderate intensity activity per day or more) may not be easily achieved at the population level.¹⁰⁸ Evidence relating to these topics has mainly been derived from a single exposure measurement. A recent review suggests that exploiting longitudinal data may improve the understanding of how interventions to decrease physical inactivity or sedentary behaviour, or both, could affect health and mortality.¹⁰⁶

There were no published systematic reviews that summarised evidence from mortality studies using repeated assessed physical activity and sedentary behaviour. Therefore, as mentioned in Chapter 1 (Section 1.3, aims and objectives), one of the aims of this thesis was to systematically summarise the evidence from these studies, including the analytic approaches and study findings. The systematic review will be presented in the next chapter.

Chapter 3 Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings

Objective 1 of the thesis is to systematically review the analytic methods and findings from mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour. To address Objective 1, I performed a systematic review of the literature. This chapter presents the authors' accepted version of the following paper published in *International Journal of Epidemiology*:

Yi Yang, Suzanne C Dixon-Suen, Pierre-Antoine Dugué, Allison M Hodge, Brigid M Lynch, Dallas R English. Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings. *International Journal of Epidemiology* 2021; dyab181, doi:10.1093/ije/dyab181

Supplementary material related to this publication is included in Appendix A.

Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings

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ABSTRACT

Background: Questions remain about the effect on mortality of physical activity and sedentary behaviour over time. We summarised the evidence from studies that assessed exposure from multiple time points and critiqued the analytic approaches used.

Methods: A search was performed on MEDLINE, Embase, Emcare, Scopus, and Web of Science up to January 2021 for studies of repeatedly assessed physical activity or sedentary behaviour in relation to all-cause or cause-specific mortality. Relative risks from individual studies were extracted. Each study was assessed for risk of bias from multiple domains.

Results: We identified 64 eligible studies (57 on physical activity, 6 on sedentary behaviour, 1 on both). Cox regression with a time-fixed exposure history (n=45) or time-varying covariates (n=13) were the most frequently used methods. Only four studies used g-methods, which are designed to adjust for time-varying confounding. Risk of bias arose primarily from inadequate adjustment for time-varying confounders, participant selection, exposure classification, and changes from measured exposure. Despite heterogeneity in methods, most studies found that being consistently or increasingly active over adulthood was associated with lower all-cause and cardiovascular disease mortality, compared with being always inactive. Few studies examined physical activity changes and cancer mortality, or effects of sedentary behaviour changes on mortality outcomes.

Conclusions: Accumulating more evidence using longitudinal data while addressing the methodological challenges would provide greater insight into the health effects of initiating or maintaining a more active and less sedentary lifestyle.

Keywords: physical activity, sedentary behaviour, mortality, longitudinal studies, time-varying exposures, time-varying confounding, g-methods.

Key Messages

- This systematic review provides an up-to-date summary of the evidence on the effects of physical activity and sedentary behaviour on mortality from cohort studies using repeated exposure assessment.
- Most studies were subject to various levels of risk of bias from time-varying confounding, selection of healthier participants, measurement error due to the questionnaire-based exposure assessment, and changes from measured exposure over long follow-up periods.
- Despite heterogeneity in methods and potential biases, being consistently active or increasing physical activity over time was found to be associated with lower all-cause and cardiovascular mortality, compared with being consistently inactive.
- Additional studies using methodologically-sound analysis of longitudinal data would help strengthen the evidence on the health benefits of being physically active.

INTRODUCTION

Insufficient physical activity (not meeting physical activity guidelines) and sedentary behaviour (time spent sitting, as distinct from lack of physical activity) both increase the risk of chronic disease and mortality. Recommended levels of physical activity to achieve these health benefits are mainly based on evidence from observational studies that assessed physical activity and sedentary behaviour at a single time point.¹⁰⁹⁻¹¹¹ The limitation of using a single assessment of exposure is that the true effects of long-term exposure will be incorrectly estimated if participants change their activity habits.^{112,113} Furthermore, questions about benefits of changing patterns of physical activity or sedentary behaviour across the life course cannot be answered with studies that assessed exposure once. To overcome this problem, some cohort studies have collected more data on exposure status after baseline, or collected recalled data for multiple time points in the past to examine the associations of time-varying physical activity and sedentary behaviour with mortality. The aims of this review were to critically appraise the analytic methods in studies that used repeated exposure assessments to examine the effects of physical activity or sedentary behaviour on all-cause or cause-specific mortality, and to systematically summarise the evidence generated from these studies.

METHODS

Eligibility criteria and search strategy

Studies were eligible for inclusion if: (1) they were observational or interventional studies published in English; (2) the exposures of interest were physical activity or sedentary behaviour assessed at two or more time points (including recalled exposure); (3) the outcome of interest was all-cause or cause-specific mortality; (4) participants were not selected based on pre-existing diseases; and (5) participants were at least 18 years old at recruitment, or exposures were recalled for age 18 years or older.

A systematic search was conducted using Ovid MEDLINE, Embase, Emcare, Scopus, and Web of Science from their inception to 20 January 2021. The search strategy was developed in consultation with University of Melbourne librarians. Search terms are listed in Supplementary Table 3-1. After removing duplicates, two reviewers (YY and one of DE, PAD, and BML) screened a sample of the search results (5900 records) independently to exclude unsuitable studies based on title and abstract and achieved 99.5% agreement. The remaining titles and abstracts were screened by one reviewer (YY). Two reviewers (YY and one of SDS and DE) independently reviewed the full text of papers in detail to assess eligibility. Disagreements were resolved by discussion. Reference lists of the included studies were manually searched for any additional relevant studies.

The protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (<https://www.crd.york.ac.uk/prospero/>, registration number CRD42019124676).

Data Extraction

From each study, two reviewers (SDS or DE, and YY) extracted the first author's name, year of publication, characteristics of the study population (country, study name, proportion of women, and age range at recruitment), sample size, details of exposure of interest, time points when exposure data were available (measured and/or recalled), outcome(s) of interest, follow-up duration, analysis method, covariates included in the models, and relative risks (RRs), which included hazard ratios, rate ratios, risk ratios and 95% confidence intervals (CIs).

For studies that assessed multiple domains of physical activity (e.g., presented estimates for household, transport, occupation, leisure-time physical activity separately), we extracted RRs

for leisure-time and/or total physical activity because these assessments were the most frequently reported across studies.

Risk of bias in individual studies

We assessed risk of bias for each study using the Risk of Bias In Non-randomised Studies – of Exposures (ROBINS-E),¹¹⁴ which is a preliminary tool adapted from the Risk of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool to suit studies of exposures.¹¹⁵ We used ROBINS-E for its ability to assess potential bias in multiple domains: confounding (particularly time-varying confounding), selection of participants, classification of exposures, departure from measured exposure (for example, due to changes in exposure between time points or during follow-up), missing data, measurement of outcomes, and selection of the reported results. The overall risk of bias for each study (low, moderate, serious, or critical) was defined as the highest risk in any individual domain. We used a causal diagram (Supplementary Figure 3-1) to guide the assessment of risk of bias from confounding.

Synthesis of results

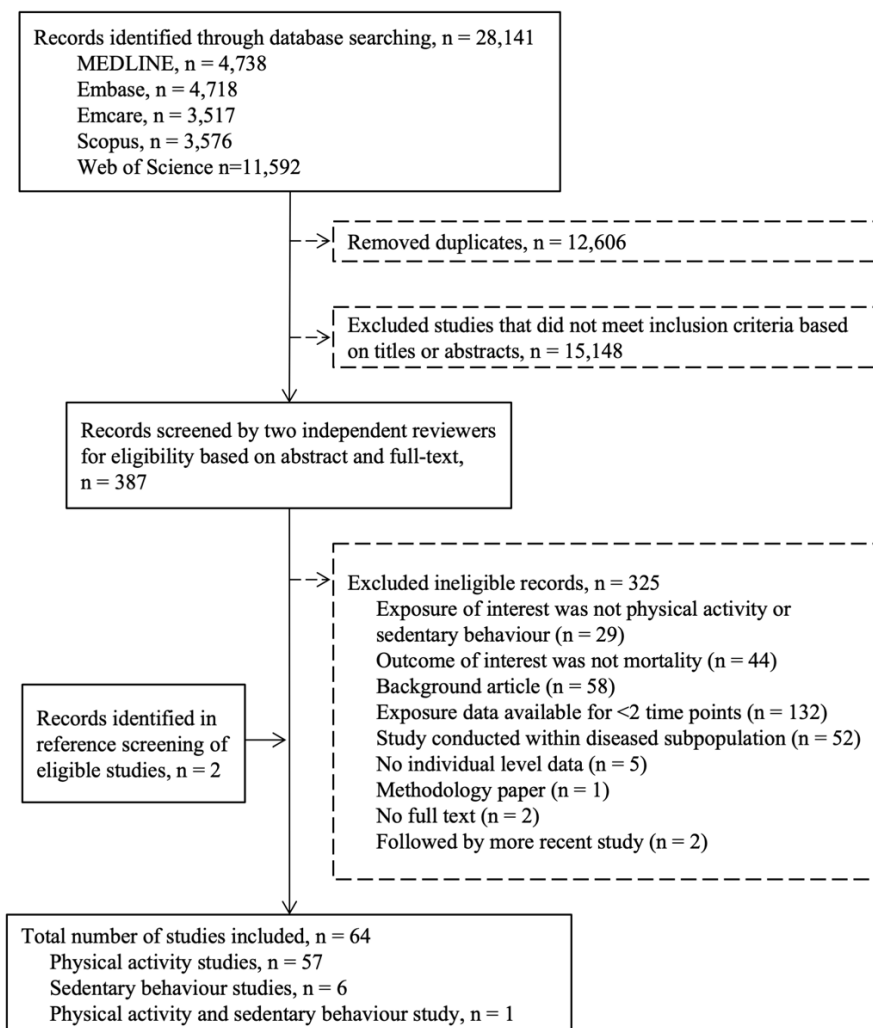
We did not perform a meta-analysis due to heterogeneity of the study samples, exposure assessment and classification, and statistical analyses. Instead, we present RRs from individual studies using structured tabulation and, where possible, graphical presentation using forest plots as recommended by Cochrane.¹¹⁶ To facilitate comparison between studies, we used ‘consistent inactivity’ or an equivalent category as the reference group. We converted RRs and CIs from studies that did not use this category as the reference using a program by Hamling and colleagues.¹¹⁷

RESULTS

Summary of the included studies

After full-text review, 64 studies were included (Figure 3-1). The number of excluded studies by primary reason for exclusion is presented in Supplementary Table 3-2. Characteristics of included studies are summarised in Table 3-1. Fifty seven studies examined physical activity,¹¹⁸⁻¹⁷⁴ six studies examined sedentary behaviour,¹⁷⁵⁻¹⁸⁰ one study examined both.¹⁸¹ Except for two intervention studies,^{151,167} all studies were prospective cohort studies.

Figure 3-1. Flowchart of study selection (systematic review)



Exposure categorisation

The two intervention studies assigned long-term physical activity programs.^{151,167} All of the cohort studies used questionnaires to assess physical activity or sedentary behaviour. Forty seven studies categorised exposure changes or maintenance with a summary variable of exposure history such as the average, change, persistence, or trajectories.^{118-121,123-126,128,129,131,133-137,140,141,143,146-152,154-157,159-162,165-167,170-173,175-179,181} Other cohort studies included separate exposure status for each data collection wave and did not combine exposure over time.

Statistical methods

The most common statistical method used to estimate mortality and adjust for confounding was regression: 45 studies used Cox regression with a time-fixed summary variable of the exposure history; 13 studies used Cox regression with time-varying covariates, three used Poisson

regression (one of these used time-varying exposure), and one used logistic regression. Two studies used marginal structural models and two used the parametric g-formula. Some studies used more than one approach. The exposure categorisation and statistical methods used in each study are summarised in Table 3-1.

Risk of bias assessment

Table 3-2 summarises results of the risk of bias assessments. Risk of bias arose mainly from confounding, selection of participants, classification of exposure, and departure from measured exposure over long follow-up periods.

Potential confounding of the effect of physical activity or sedentary behaviour on mortality arose from the following domains: demographic attributes, health-related factors or comorbidities that affect both the exposure and mortality, adiposity, and other lifestyle co-exposures that are also risk factors of mortality. When these confounders vary over time and are affected by prior exposure, they could also be mediators (see Supplementary Figure 3-1). Because this review focused on effects of exposure over time, bias from inadequate adjustment of time-varying confounding was considered. Most studies were graded as having moderate to serious risk of bias due to confounding, because the analyses did not adjust for several important confounders, and/or did not adequately adjust for their time-varying confounding effect. Similarly, risk of bias from participant selection was graded as moderate to serious for most studies, mainly because selection of participants into the analysis was determined by post-exposure vital status (i.e., collider bias). Most studies had at least moderate risk of bias due to misclassification of the exposure because of the use of self-reported physical activity and sedentary behaviour, except the two intervention studies, where a physical activity intervention was assigned.^{151,167} About two thirds of the studies were graded as having moderate risk of bias due to departures from measured exposure, because exposure data were not updated over long follow-up periods. Missing data, outcome ascertainment, and selection of reported results were assessed as introducing minimal bias in most studies.

Changes in physical activity over time and mortality

The time between the first and last assessment of physical activity ranged from 12 months to 40 years. Associations between changes in physical activity and all-cause mortality are presented in Figure 3-2 (total physical activity) and Figure 3-3 (leisure-time physical activity). Compared with consistent inactivity, stable or increasing amounts of total and leisure-time physical activity were associated with lower all-cause mortality, while decreasing amounts of

leisure-time physical activity were associated with higher all-cause mortality. Similar associations were observed for cardiovascular disease (CVD) mortality (Figure 3-4). Only five studies examined cancer mortality (four examined all-cancer mortality, one examined colon cancer mortality); RRs were generally smaller than for all-cause and CVD mortality (Figure 3-5).

Results from studies using other techniques to incorporate data across multiple time points that did not report RRs for changes in physical activity are presented in Supplementary Table 3-3. These studies used averaged physical activity levels as the exposure or updated physical activity in Cox regression with time-varying covariates, and generally showed lower mortality for higher levels of physical activity.^{124,125,127,132,138,139,142,145,153,163,166,168,171,174}

Of the six studies that studied changes in physical activity and were graded as having only moderate risk of bias,^{124,151,165,167,171,181} five examined all-cause mortality, and found moderately lower risk in participants with consistently high total^{165,167,171} or leisure-time^{124,181} physical activity. Shortreed et al.¹⁶⁵ found that being consistently active over 40 years in adulthood was associated with moderately lower all-cause mortality than being consistently inactive (RR=0.81, 95% CI [0.71, 0.93]). Williamson et al.¹⁷¹ also found lower all-cause mortality under a simulated eight-year intervention of high compared with low physical activity (RR=0.73, 95% CI [0.63, 0.83]). Byberg et al. reported lower all-cause mortality in participants with 10-year unchanged high leisure-time physical activity (RR=0.75, 95% CI [0.64, 0.89]) compared with those whose activity remained low.¹²⁴ Yang et al. similarly found lower all-cause mortality under a 7-year hypothetical intervention of high leisure-time physical activity (RR=0.66, 95% CI [0.46, 0.86]) compared with a “low leisure-time physical and high TV viewing” scenario.¹⁸¹ Two studies examined CVD mortality.^{151,165} Shortreed et al.¹⁶⁵ found lower CVD mortality for 30-year activity compared with inactivity (RR=0.83, 95% CI [0.72, 0.97]). Newman et al. reported that a 2.6-year physical activity intervention that involved weekly walking and strength training reduced CVD mortality compared with a health education intervention. However, the CIs were wide due to few observed deaths.¹⁵¹

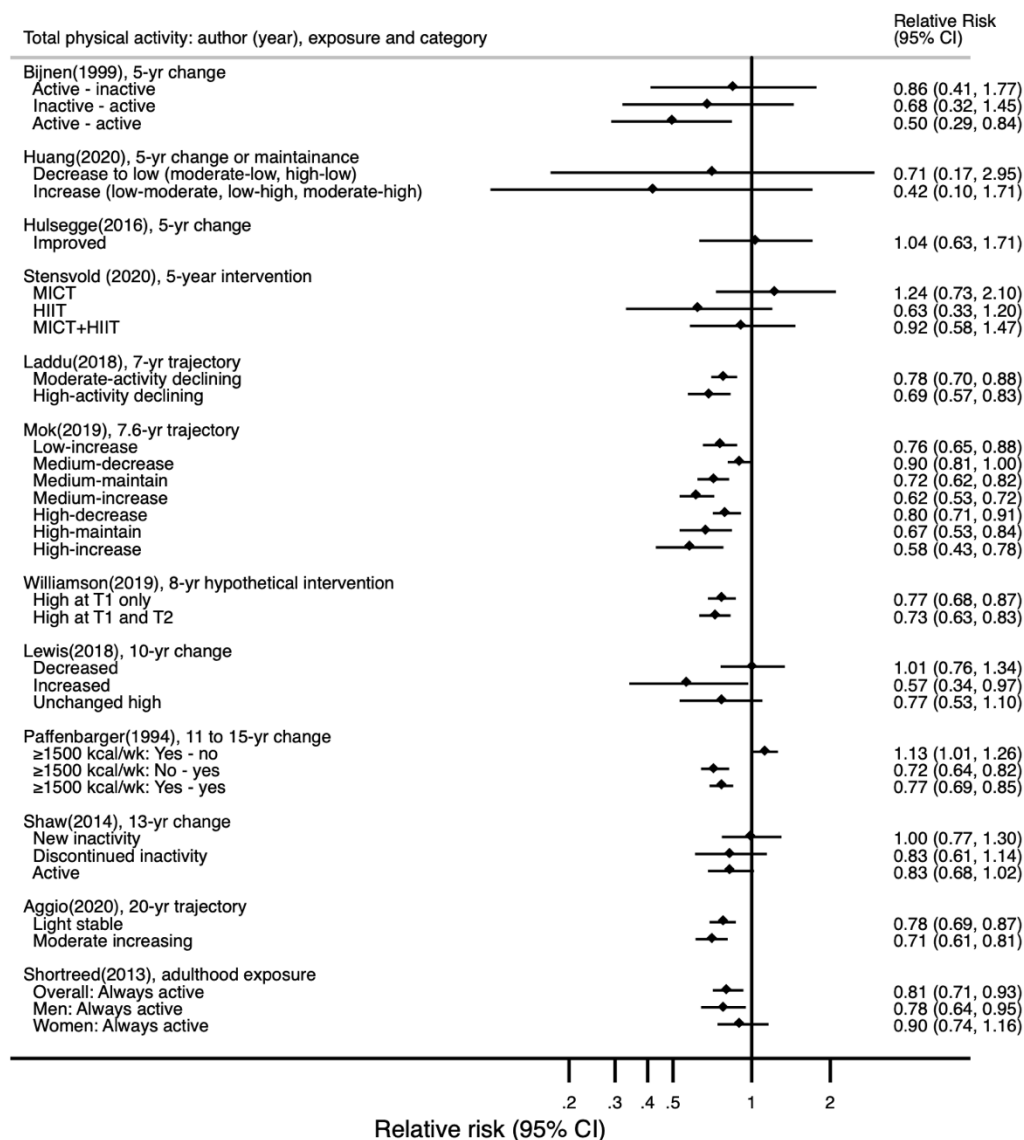
Several studies found that initiating an active lifestyle had similar survival benefits to those for persistent activity.^{120,126,146,149,156,157,159}

Changes in sedentary behaviour over time and mortality

Four of the seven studies used daily overall sitting time as a measure of sedentary behaviour, one used occupational sitting time and two used daily TV viewing time. The time between the

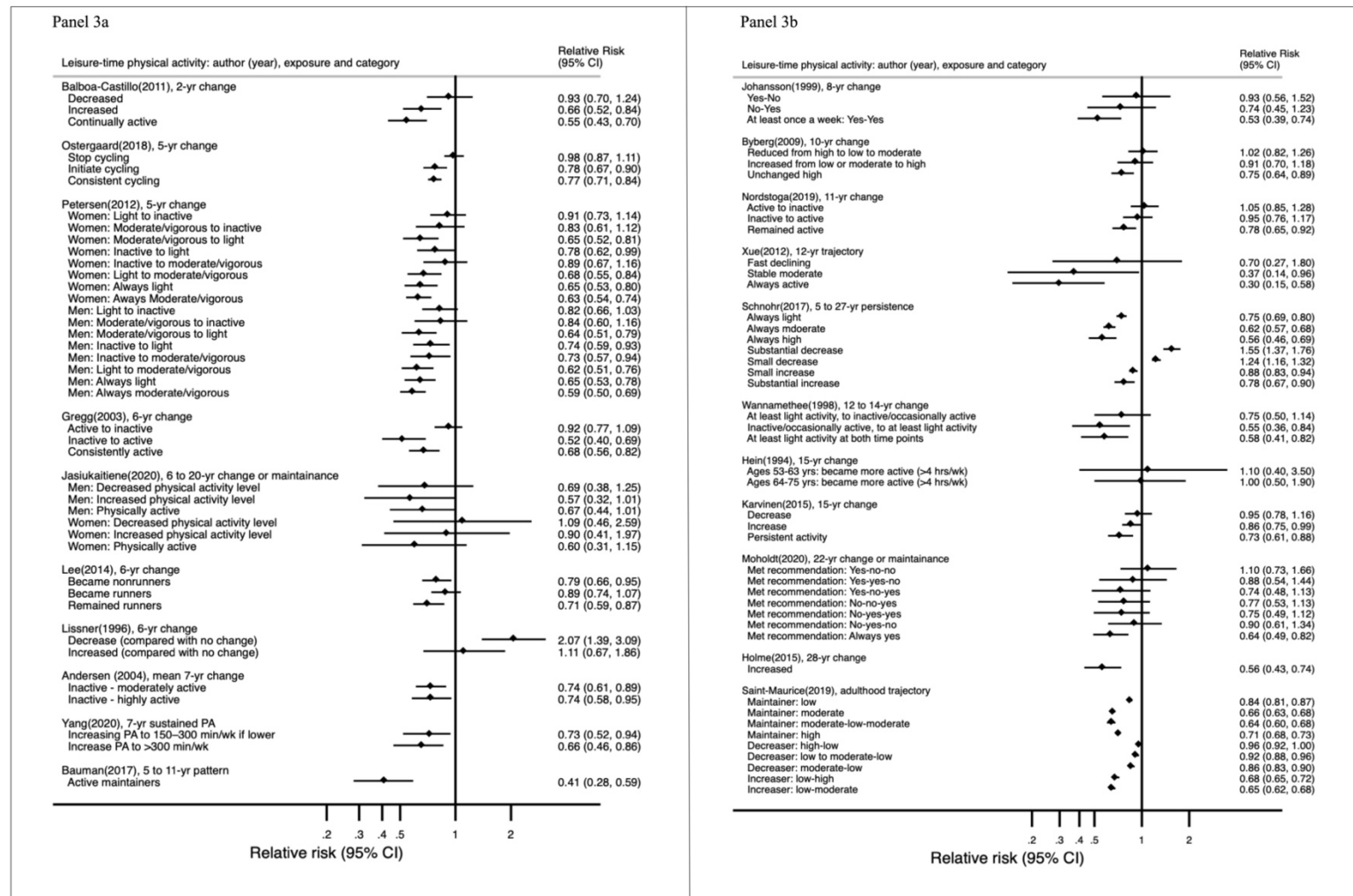
first and last assessment of sedentary behaviour ranged from two to 15 years. Changes in sedentary hours were classified using different cut-offs across the studies (Table 3-3). Six of the seven studies reported all-cause mortality, three reported CVD mortality, and one reported cancer mortality. All but one study reported RRs for changes in sedentary behaviour.¹⁸⁰ Maintaining low sitting or TV viewing time was generally associated with lower all-cause, CVD and cancer mortality, compared with having a consistently sedentary lifestyle (Table 3-3).

Figure 3-2. Forest plot of relative risks for changes in physical activity (total) in relation to all-cause mortality, compared with consistent inactivity



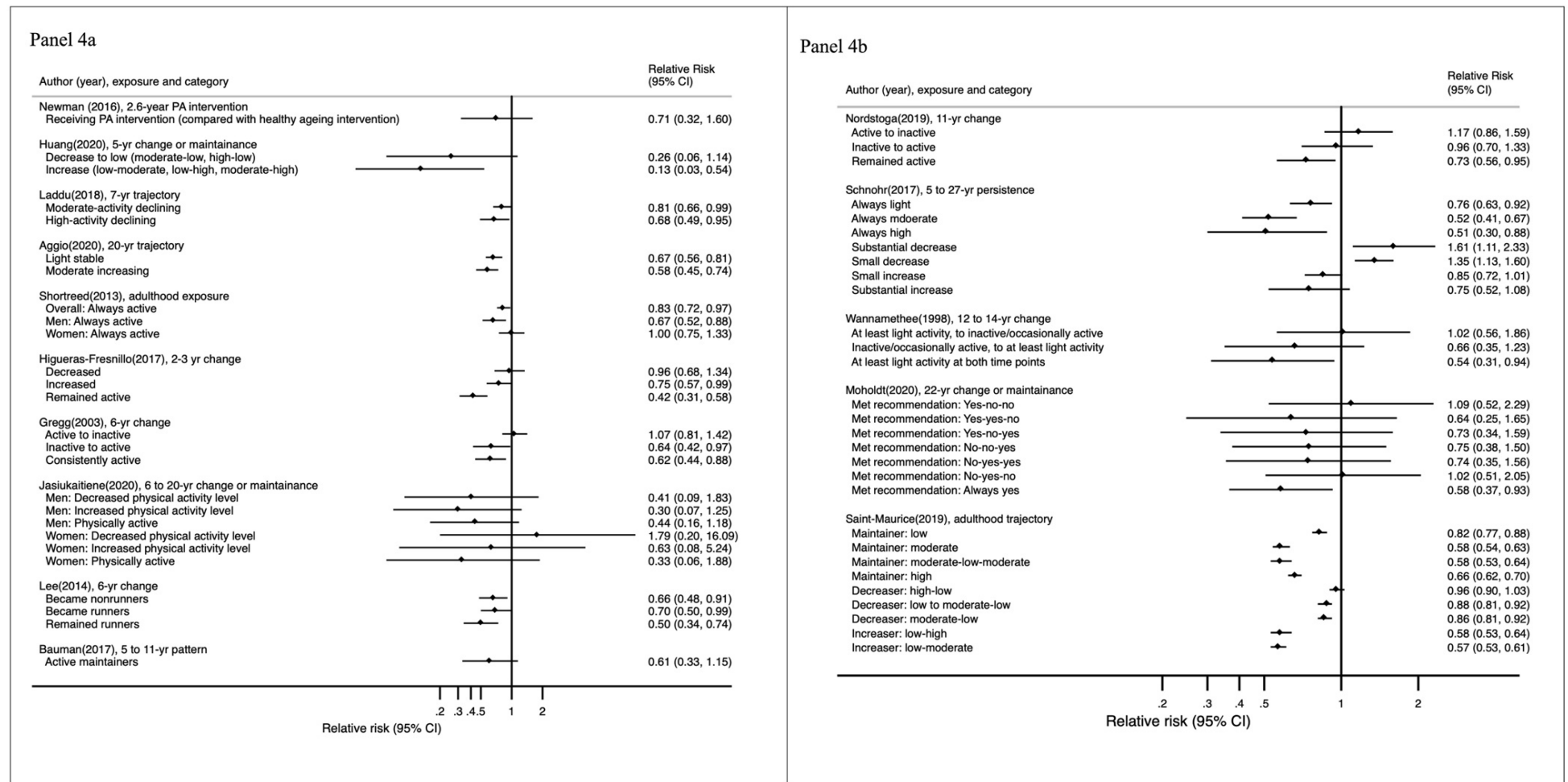
MICT: moderate intensity continuous training; HIIT: high intensity interval training. Shortreed et al. reported marginal rate ratios. Williamson et al. reported risk ratios. Other studies reported hazard ratios. Presented by ascending order of the duration between first and last exposure assessment.

Figure 3-3. Forest plot of relative risks for changes in physical activity (leisure-time) in relation to all-cause mortality, compared with consistent inactivity



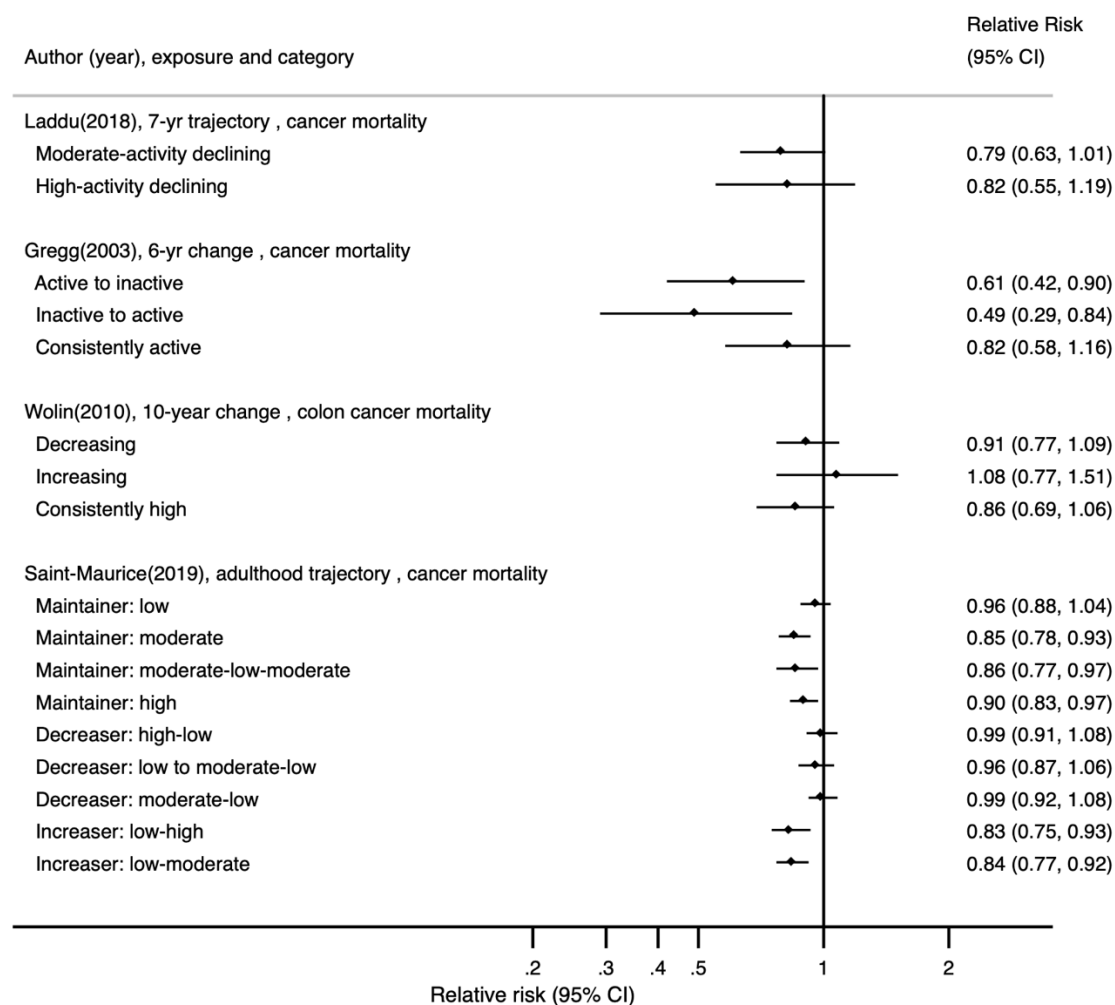
Yang et al. reported risk ratios using “Low leisure-time PA and watching 2+ h/d TV” as reference. Hein reported odds ratios. Other studies reported hazard ratios. Presented by ascending order of the duration between first and last exposure assessment.

Figure 3-4. Forest plot of relative risks for changes in physical activity (total or leisure-time) in relation to cardiovascular mortality, compared with consistent inactivity



Shortreed et al. reported marginal rate ratios. Other studies reported hazard ratios. Newman et al. examined PA intervention; Laddu et al., Aggio et al. and Shortreed et al. examined total physical activity; other studies examined leisure-time physical activity.

Figure 3-5. Forest plot of relative risks for changes in physical activity (total or leisure-time) in relation to cancer mortality, compared with consistent inactivity



All studies reported hazard ratios. Laddu et al. examined total physical activity. Other studies examined leisure-time physical activity.

DISCUSSION

The studies reviewed found that consistent and increasing levels of physical activity over time were associated with lower all-cause and CVD mortality, compared with being consistently inactive, although study designs were heterogeneous and often carried substantial risk of bias. Few studies examined the effects of changes in physical activity on cancer mortality, or of changes in sedentary behaviour on any mortality outcome. Cox regression (with or without adjustment for time-varying covariates) was the method most commonly used to estimate associations with mortality.

Although findings from the included studies were not directly comparable due to the diversity of exposure classification, time between first and last exposure assessment, duration of passive follow-up, analysis method and adjustment factors, most included studies suggested a moderate survival benefit from maintaining an active lifestyle over the long term. This is consistent with findings from studies that assessed physical activity at a single time point. A systematic review and meta-analysis of 80 cohort studies¹⁰² found that higher levels of total and domain-specific activity were associated with reduced all-cause mortality (RRs corresponding to 150 and 300 min/week of moderate to vigorous activity were 0.86, 95% CI [0.80, 0.92] and 0.74, 95% CI [0.65, 0.85], respectively, compared with the lowest level of activity). The risk reduction was greater for vigorous exercise and sports (RR=0.78, 95% CI [0.72, 0.88] for 150 min/week, and RR=0.61, 95% CI [0.51, 0.74] for 300 min/week). A pooled analysis of leisure-time physical activity and mortality using data from six studies in the National Cancer Institute Cohort Consortium observed lower mortality risk (RR 0.69, 95% CI [0.67, 0.70]) for participants achieving one or two times the recommended minimum of 7.5 metabolic-equivalent (MET) hours per week compared with participants reporting no leisure-time physical activity.¹⁸²

Decreasing physical activity or increasing sedentary behaviour levels over time were associated with higher mortality in some studies,^{147,156,161,175-177} although the observed associations may have been confounded by other time-varying variables, such as deteriorating health, that is a common reason for behavioural changes and death.

Potential sources of bias

The potential biases present in the included studies need to be considered when interpreting the results of this systematic review. A major source of bias in all studies came from measurement error when using questionnaire-based exposure assessments; this methodological issue has well known effects on the risk estimates generated from observational studies on physical

activity.^{106,183,184} Some of the questionnaires were not validated and were therefore potentially susceptible to yet higher risk of bias from measurement error or misclassification of physical activity level and sedentary behaviour. Although repeated accelerometry measurements are not yet available for large-scale cohort studies, accelerometry data from a single time point have been used in several recent studies. A harmonised meta-analysis of these studies¹³ showed substantially lower mortality risk associated with high physical activity and low sedentary hours than reported in studies using questionnaire-based exposure data.^{14,102,182} The most active quarter as measured using accelerometers was associated with markedly lower all-cause mortality (RR=0.27, 95% CI [0.23, 0.32]), compared with the least active quarter. Longer accelerometer-measured sedentary time was also associated with substantially higher all-cause mortality (RR=2.63, 95% CI [1.94, 3.56]) comparing the most with the least sedentary quarter.¹³ This suggests that imperfect exposure assessment by questionnaires likely underestimates the beneficial effect of an active lifestyle.

More than half of the included studies followed participants for more than 10 years. Despite exposure assessments at multiple time points, unrecorded changes in physical activity and sedentary behaviour could have occurred during long follow-up periods, contributing to risk of bias due to departures from measured exposure. Some studies updated exposure information in Cox regression with time-varying covariates. However, the effect of broad exposure changes over time (e.g. increased/decreased physical activity levels) cannot be estimated using this approach.

Another methodological challenge is that the conventional approach of adjusting for confounders in regression models may introduce bias.^{185,186} This is because in those studies where exposures and confounders were assessed at least twice, the repeatedly assessed confounders were likely affected by prior exposures. For example, as shown in Supplementary Figure 3-1, when estimating the joint effect of physical activity or sedentary behaviour measured at two time points on mortality, body size at time 2 was a confounder (i.e., people who were obese at time 2 were less likely to be active and had higher risk of death) hence it should be adjusted for. However, body size at time 2 was also a result of physical activity at time 1. In this scenario, adjustment for body size blocks the part of the effect of physical activity at time 1 that is mediated by body size at time 2 (i.e., overadjustment bias¹⁸⁶). This scenario is illustrated in Supplementary Figure 3-2, using physical activity in a two-time-point setting. In studies using Cox regression with a time-fixed summary variable of physical activity history, confounders measured at the final time point and/or confounders at earlier time points (i.e., L₁

and/or L_0 in Supplementary Figure 3-2) were typically adjusted for. Similarly, studies using Cox regression with time-varying covariates updated and adjusted for confounders at all available time points (i.e., L_0 and L_1). Conditioning on the intermediate variable L_1 blocks some of the causal pathways from physical activity to death (e.g. $PA_0 \rightarrow L_1 \rightarrow VS_2$, and $PA_0 \rightarrow L_1 \rightarrow PA_1 \rightarrow VS_2$). As a result, the joint effect of PA_0 and PA_1 may be underestimated. Furthermore, selection bias (i.e., collider stratification bias) can occur if a time-varying confounder that shares a common cause with the outcome is adjusted for using conventional regression methods.¹⁸⁶

This type of bias may also affect randomised controlled trials. The two intervention studies considered in our review randomised participants to physical activity interventions or comparator groups, which avoids baseline confounding (L_0), but not post-baseline confounding (L_1), potentially affecting both the adherence to the assigned intervention and risk of death from CVD.^{151,167} Only four studies^{122,165,171,181} used g-methods (marginal structural models or the parametric g-formula), which do appropriately adjust for time-varying confounding.^{186,187}

Bias due to selection of participants is another concern when examining effects of physical activity or sedentary behaviour over time on mortality, as illustrated in Supplementary Figure 3-3. In studies using Cox regression with a summary variable of exposure history, follow-up often started at the final time point. Selection of participants was therefore determined by whether an individual had enough data points to derive the summary exposure variable, which was likely to be affected by participants' activity level (e.g. participants who are more active are more likely to return for follow-up visits) and other confounders (e.g. generally healthier participants are more likely to return). Selection was also determined by vital status at the final time point. These forms of selection bias (collider bias) might have biased effect estimates towards the null.¹⁸⁸

In future research, the aforementioned biases could be reduced at the stage of study design or development of the statistical analysis plan. With regards to biases incurred at the study design stage, frequent data collection intervals across the follow-up period could help avoid unrecorded changes of the exposures and confounders. The exposure assessments will eventually be improved as more objective measurement methods are increasingly being incorporated into cohort studies. At the data analysis stage, studies should avoid selecting participants into the analysis based on their health or vital status to reduce selection bias. Statistical methods such as the g-methods should be used to account for time-varying confounding affected by prior exposures. Randomised controlled trials, often viewed as the

ideal design for causal inference, would also benefit from more sophisticated statistical methods to adjust for post-randomisation confounding and selection biases when estimating the per-protocol effect of long-term interventions.¹⁸⁹ Studies addressing these methodological concerns are needed to improve our understanding of the potential survival benefits of initiation or maintenance of a more active and less sedentary lifestyle.

In conclusion, our review provides an up-to-date summary of the evidence relating to physical activity, sedentary behaviour, and mortality from studies using repeated exposure assessment. Greater insight incorporating changes over time in physical activity and sedentary behaviour is important for refining public health guidelines and recommendations related to physical activity and sedentary behaviour. Although conclusions from these studies did not differ qualitatively from those based on studies of exposure at one time point, we highlighted some methodological challenges in studies examining repeated exposure measurements that could have biased the results of the included studies.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its supplementary material.

SUPPLEMENTARY DATA

Supplementary data are available at *International Journal of Epidemiology* online (and in Appendix A of this thesis).

FUNDING

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CONFLICT OF INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All authors participated in developing the systematic review protocol. YY, SCDS, PAD, BML and DRE participated in titles and abstract screening. YY, SCDS and DRE reviewed full texts for study eligibility, extracted the data and performed risk of bias assessment for the included studies. All authors helped to draft the manuscript and revised it critically. All authors read and approved the final manuscript.

Table 3-1. Summary of study characteristics included in the systematic review

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Studies examining physical activity									
Aggio, 2020	United Kingdom; British Regional Heart Study; 0% women; 40–59 years	Total PA	20-year trajectory categorised using GBTM	Baseline; 12-year, 16-year, 20-year follow-ups	All-cause [1735; 3231] CVD [610; 3231]	Median 16.4 years, from the 20-year follow-up to 2016	Cox regression	Age, occupational class, marital status, alcohol consumption, smoking, LDL, HDL, SBP, insulin, waist circumference and FEV1	Hazard ratio
Andersen, 2004	Denmark; Pooled data from the Copenhagen City Heart Study, Glostrup Population Studies, and Copenhagen Male Study; 49% women; 20-93 years	Leisure-time PA	Mean 7-year change or maintenance	2 time points starting 1964, average 7 years apart	All-cause [932; 6960]	Mean 10.8 years (women) and 9.6 years (men), from the second time point	Cox regression	Age and sex (authors reported that adjustment for total cholesterol, SBP, education, smoking, and BMI did not change the results)	Hazard ratio
Balboa-Castillo, 2011	Spain; A cohort study of the non-institutionalised Spanish population; 57% women; ≥60 years	Leisure-time PA	2-year change or maintenance	2001, 2003	All-cause [505; 2732]	6 years from 2003	Cox regression	Sex, age, education, smoking, alcohol, CHD, stroke, cancer, COPD, diabetes, hip fracture, SF36 physical summary, Mini-Mental State Examination, BMI, waist circumference, limitations in mobility, agility, and in instrumental ADLs	Hazard ratio
Bauman, 2017	Denmark; Danish MONICA (MONItoring Trends and Determinants in Cardiovascular Disease); 49% women; 30-61 years	Leisure-time PA	5 to 11-year pattern	1982, 1987 (if available), 1993	All-cause [445; 2412] CVD [185; 2412] CHD [69; 2412]	Up to 14 years from 1993 to 2007	Cox regression	Age, sex, and education	Hazard ratio
Bombom, 2009	United States; The Study of Physical Performance and Age-related Changes in Sonomans; 53% women; ≥54 years	Leisure-time PA	Counterfactual exposure weighted averages across 4 time points	1993-1994, 1995-1996, 1998-1999, 2000-2001	All-cause [235; 5233]	2 years following a given survey	History-adjusted marginal structural model	Time-fixed: past PA, sex, baseline reported exposure to environmental tobacco smoke, time-varying: BMI, having at least 1 chronic disease, depression score, current use of antidepressant, smoking, overall health, living arrangements, and functional limitation	Excess risk
Bijnen, 1999	The Netherlands; The Zutphen Elderly Study; 0% women; 65-85 years	Total PA	5-year change or maintenance	1985, 1990	All-cause [118; 472]	5 years from 1990	Cox regression	Age, prevalence of disease (CVD, cancer, chronic nonspecific lung diseases, diabetes mellitus), functional status, cigarette smoking, and alcohol intake in 1990.	Hazard ratio
Byberg, 2009	Sweden; Uppsala longitudinal study of adult men (ULSAM); 0% women; 49-51 years	Leisure-time PA	1) 10-year change or maintenance; 2) 35-year time-varying exposure	1) ages 50, 60; 2) ages 50, 60, 70, 77, 82	All-cause [1] 998; 1759 2) 1329; 2205]	1) 26 years from age 60; 2) 35-years from age 50	1) Cox regression; 2) Cox regression with time-varying covariates	1) Smoking, obesity, height and weight, self-perceived health, PA at work, diabetes, any musculoskeletal, neurological, or psychiatric disorders, and alcohol use; 2) covariates in 1) and BP, use of antihypertensive drugs, total serum cholesterol, education, and socioeconomic group.	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Emberson, 2005	United Kingdom; British Regional Heart Study; 0% women; 40–59 years	Leisure-time PA	20-year average	1978-1981, 1992, 1996, 1998-2000	All-cause [1525; 6452]	20 years from 1978-1981	Cox regression	Age	Hazard ratio
Gregg, 2003	United States; The Study of Osteoporotic Fractures (SOF); 100% women; ≥ 65 years	Leisure-time PA	6-year change or maintenance	1986-1988, 1992-1994	All-cause [1029; 7553] CVD [386; 7553] Cancer [264; 7553]	Up to 6.7 years from 1992-1994	Cox regression, also estimated and stratified by propensity scores	Age, smoking, BMI, stroke, diabetes, hypertension, self-rated health status, CHD, cancer, COPD, incident hip fracture, and baseline PA	Hazard ratio
Hamer, 2014	United Kingdom; The English Longitudinal Study of Ageing; 54% women; ≥ 50 years	Total PA	6-year time-varying exposure	2002-2003, 2004-2005, 2006-2007, 2008-2009	All-cause [1896; 10426] CVD [671; 10426] Cancer [596; 10426]	Mean 7.8 years from 2002–2003	Cox regression with time-varying covariates	Age, gender, marital status, socioeconomic position, time-varying covariates (chronic diseases, smoking, depressive symptom, BMI, and waist circumference)	Hazard ratio
Hein, 1994	Denmark; the Copenhagen Male Study; 0% women; 40-59 years	Leisure-time PA	15-year change or maintenance	1970-1971, 1985-1986	All-cause [270;2894]	6 years from 1985/1986	Logistic regression	Analysis stratified by age (53-63 years, and 64-75 years).	Odds ratio
Higuera-Fresnillo, 2017	Spain; Universidad Autónoma de Madrid (UAM) cohort; 57% women; ≥ 60 years	Leisure-time PA	2- to 3-year change or maintenance	2000-2001, 2003	CVD [467; 2836]	Mean 9 years from 2003 to 2014	Cox regression	Age, sex, education, smoking, alcohol, subjective health, Mini-Mental State examination, BMI, SBP, hypercholesterolemia, agility disability, mobility disability, limitation in instrumental ADLs, and the following self-reported diseases diagnosed: asthma/bronchitis, CHD, stroke, diabetes, depression, hip fracture, and cancer.	Hazard ratio
Hirvensalo, 2000	Finland; Evergreen Project; 65% women; 65-84 years	Total PA	baseline exposure adjusted for recalled past activity	1988 (baseline), recalled: age 10-19, 20-39, and 40-64 years	All-cause [389; 1109]	8 years from baseline	Cox regression	Age, gender, marital status, education, presence of asthma, diabetes, neurological diseases, stroke, mental diseases, CVD, musculoskeletal diseases, smoking and past PA.	Hazard ratio
Holme, 2015	Norway; The Oslo study (Oslo I and II); 0% women; 40-49 years	Leisure-time PA	28-year change or maintenance	1972-1973, 2000	All-cause [2154; 5738]	12 years from 2000 to 2011	Cox regression	Age, education, smoking, diabetes, previous MI, and previous stroke	Hazard ratio
Hsu, 2018	Australia; The Concord Health and Aging in Men Project (CHAMP); 0% women; ≥70 years	Total PA	5-year temporal change	2005-2007; 2-year and 5-year follow-up	All-cause [519; 1705] CVD [185; 1705] Cancer [151; 1705]	Median 7 years from baseline (2005-2007)	Poisson regression with generalized estimating equations (GEE)	Age, comorbidity, smoking, alcohol, BMI, ethnicity, education, CVD, diabetes, self-rated health, and ADL disability, and depression (model for CVD mortality did not adjust for CVD)	Rate ratio
Huang, 2020	China; Guangzhou Biobank Cohort Study; 73% women; mean age 61 years	Total PA	5-year change or maintenance	2003-2008 (baseline); 2008-2012 (follow-up)	All-cause [1461; 18104] CVD [703; 18104]	Mean 7.8 years from the follow-up (2008-2012) to Dec 2017	Cox regression	Sex, age, occupation, personal income, education, alcohol use, smoking, and self-rated health.	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Huerta, 2016	Spain; European Prospective Investigation into Cancer and Nutrition study - Spanish branch (EPIC-Spain); 62% women; 30-65 years	Leisure-time PA	3.3-year average	1992-1996, 1996-1999	All-cause [1371; 38379] CVD [291; 38379] Cancer [758; 38379]	Mean 13.6 years from 1992-1996	Cox regression	Centre, baseline education, height, weight, waist and hip circumferences, self-reported hypertension or hyperlipidemia, diabetes, smoking, alcohol, total energy intake, and Mediterranean diet score, and mutual adjustment of all PA variables (work, household, and recreational PA)	Hazard ratio
Hulsegge, 2016	The Netherlands; The Doetinchem Cohort Study; 54% women; 26-66 years	Total PA	5-year change or maintenance	1993-1997, 1998-2002	All-cause [338; 5263]	12.2 years from 1998-2002 to 2013	Cox regression	Age, sex, education, occupation, BMI, smoking, Mediterranean diet score, and alcohol consumption	Hazard ratio
Jasiukaitiene, 2020	Lithuania; Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study; 56% women; 35-64 years (mean age 47.3 years men, 47.4 years women)	Leisure-time PA	Change or maintenance between two time points	One of the initial surveys (1986-1987, 1992-1993, 2001-2002); 2006-2008	All-cause [382; 2416] CVD [67; 2416 minus prevalent CVD cases]	Mean 10.6 years, from 2006 (the follow-up survey)	Cox regression	Baseline age, education and biological factors (i.e., systolic blood pressure, total cholesterol, triglycerides, fasting glucose, body mass index), smoking status.	Hazard ratio
Johansson, 1999	Sweden; Swedish Annual Level-of-Living Survey; 51% women; 25-74 years	Leisure-time PA	8-year change or maintenance	1980-1981, 1988-1989	All-cause [357; 3843]	6 years from 1988-1989	Cox regression	Sex, age, marital status, education, smoking, overweight, BMI, hypertension	Hazard ratio
Joseph, 2020	Denmark; The Copenhagen City Heart Study; 54% women; 20-98 years	Leisure-time PA	27-year time-varying exposure	1976-1978, 1981-1983, 1991-1994, 2001-2003	All-cause [13355; 18890]	Mean 21 years, from baseline	Cox regression with time-varying covariates	Age, sex, smoking status, education, diabetes, previous CVD, BMI, and calendar time. The covariates were revised each time an individual participated in a new examination. Stratified by BP.	Hazard ratio
Kaplan, 1996	United States; The Alameda County Study; 54% women; 16-94 years	Leisure-time PA	18-year time-varying exposure	1965, 1974, 1983	All-cause [1226; 6131] CVD [709; 6131]	28 years from 1965	Cox regression with time-varying covariates	Age, sex, ethnicity and time-varying covariates (education, health conditions, smoking, BMI, and social isolation)	Hazard ratio
Karvinen, 2015	Finland; The Finish Twin Cohort; 55% women; 18-45 years	Leisure-time PA	1) 15-year change or maintenance; 2) 15-year average	1975, 1981, 1990	All-cause [1478; 10408]	23 years from 1990 to 2013	Cox regression	Sex, age, education, smoking status in 1990, alcohol consumption, BMI in 1990, work activity, Somatic Disease Index (self-reporting any doctor-diagnosed disease, or life event causing serious illness or injury, or self-reported permanent work disability) in 1990	Hazard ratio
Laddu, 2018	United States; The Osteoporotic Fractures in Men (MrOS) Study; 0% women; ≥65 years	Total PA	7-year trajectory categorised using GBTM	at least 3 for who returned to 2007-2009 visit: 2000-2002, 2003-2005, 2005-2006, 2007-2009	All-cause [1435; 3767] CVD [484; 3767] Cancer [343; 3767]	Mean 7 years from year 7 visit	Cox regression	Age, race, clinic site, alcohol, depression, cognitive function, marital status, education, self-rated health, any one co-morbidity (COPD, stroke, MI, congestive heart failure, Parkinson's, diabetes), smoking, and BMI	Hazard ratio
Lantz, 2010	United States; Americans' Changing Lives longitudinal study; 53% women; 60+ years	Total PA	15- year time-varying exposure	1986, 1989, 1994, 2001-2002	All-cause [1409; 3617]	Up to 19 years from 1986	Cox regression with time-varying covariates	Age, gender, race, residence, education, income, smoking, alcohol use, and health status	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Lee, 2014	United States; The Aerobics Center Longitudinal Study; 26% women; 18-100 years	Leisure-time running	Mean 6-year change or maintenance	2 between 1974 and 2002	All-cause [1398;20647] CVD [490;19739]	From the last time point (length not reported)	Cox regression	Age, sex, examination year, time between baseline and last examination, and baseline smoking status, alcohol consumption, other non-running PA, and parental CVD	Hazard ratio
Lee, 2003	USA; The College Alumni Health Study (pooled two studies: Harvard University and University of Pennsylvania); 7% women; Mean 47 years	Total PA	33-year time-varying exposure	Harvard alumni:1962 or 1966, 1977, 1988, 1993. Pennsylvania alumni: 1962, 1980, 1993	Pancreatic Cancer [212; 32687]	Up to 33 years from 1962 to 1995	Cox regression with time-varying covariates	Age, sex, smoking, and diabetes	Hazard ratio
Lee, 2004	United States; The Harvard Alumni Health Study; 0% women; Mean 66 years	Total PA	5-year time-varying exposure	1988, 1993	All-cause [1234; 8421]	9 years from 1988 to 1997	Cox regression with time-varying covariates	Age, smoking, alcohol, red meat intake, vegetable intake, vitamin/mineral supplements, and early parental mortality	Hazard ratio
Lewis, 2018	United States; Hispanic Established Population for the Epidemiologic Study of the Elderly (H-EPESE); 63% women; ≥67 years	Total PA	10-year change or maintenance	1995/1996, 2005/2006	All-cause [367; 803]	7 years from 2005/2006	Cox regression	Age, gender, marital status, education, smoking, PA groups, BMI, depressive symptoms, cognition, functional disability, and comorbidities	Hazard ratio
Lissner, 1996	Sweden; The Gothenburg Prospective Study of Women; 100% women; 38-60 years	Leisure-time PA	1) 6-year change or maintenance; 2) adulthood average	1) 1968/1969, 1974/1975; 2) ages 20-38, age 39 to 60, 1968/1969	All-cause [1) 110; 1267 2)147;1405] CHD [1) n.r. 2) 22;1405]	1) 14 years from 1974/1975; 2) 20 years from 1968/1969	Cox regression	1) Adulthood activity index, initial age, baseline levels of and 6-year changes in smoking, serum triglycerides, BMI, waist hip ratio, and BP; 2) age, smoking, waist hip ratio, peak expiratory flow, BP, and serum triglycerides	Hazard ratio
Moholdt, 2020	Norway; The HUNT Study; 51 to 54% women; age 20 years or older	Leisure-time PA	Change or maintenance of PA based on guidelines between: HUNT1 and 2; HUNT1 and 3; HUNT2 and 3; HUNT1, 2, and 3.	1984–86 (HUNT1); 1995–97 (HUNT2); 2006–08 (HUNT3)	HUNT1 and 2: All-cause [7749; 32811] CVD [3064; 32811] HUNT1 and 3: All-cause [1498; 22058] CVD [494; 22058] HUNT2 and 3: All-cause [1635; 31948] CVD [516; 31948] HUNT1, 2, and 3: All-cause [1255; 19349] CVD [399; 19349]	HUNT1 and 2:18 years; HUNT1 and 3:7 years; HUNT2 and 3:7years; HUNT1, 2, and 3:7years	Cox regression	Age, sex, education, smoking, occupational PA, SBP, diabetes, BMI. Apart from age, sex, and ed, all covariates from last survey	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Mok, 2019	United Kingdom; EPIC-Norfolk cohort; 57% women; 40-79 years	Total PA	7.6-year trajectory	At least baseline and final follow-up: 1993-1997 (baseline), 1.7-year, 3.6-year, and 7.6-year follow-ups	All-cause [3148; 13360] CVD [950; 13360] Cancer [1091; 13360]	Median 12.5 years; from the final follow-up	Cox regression; Linear regression against elapsed time	Age, sex, smoking, education, social class, self-rated health, alcohol intake, energy intake, diet quality, comorbidities (CVD, cancer, diabetes, asthma, COPD, and bone fractures), BMI, BP, triglycerides, LDL, HDL cholesterol, and time-updated for lifestyle and health-related variables at second visit	Hazard ratio
Myers, 2004	United States; Subsample from men referred for exercise testing for clinical reasons between 1987 and 2000; 0% women; Mean 59 years	Leisure-time PA	lifetime exposure	Current PA collected between 1987 and 2000, past PA recalled, period not reported	All-cause [89; 842]	Mean 4.6 years, SD 1.8 years	Cox regression	Age.	Hazard ratio
Newman, 2016	United States; The Lifestyle Interventions and Independence for Elders (LIFE) study; 67% women; 70-89 years	Weekly PA intervention	2.6-year intervention	At randomisation, and weekly attendance	CVD [24; 1635]	2.6 years from randomisation	Cox regression	Randomisation stratified by clinical site and sex (randomisation stratified by these 2 variables)	Hazard ratio
Nordstoga, 2019	Norway; The HUNT Study (HUNT1 and HUNT2); 52% women; ≥ 20 years	Leisure-time PA	11-year change or maintenance	1984-1986, 1995-1997	All-cause [8449; 34257] CVD [3264; 34257]	Median 17 years, from the second visit	Cox regression	Age, sex, education, smoking status, alcohol consumption, insomnia symptoms, and history of CVD. Stratified by weight change between two waves (loss, stable, gain)	Hazard Ratio
Opdal, 2020	Norway; the Tromsø Study; 52% women; 25-79 years	Leisure-time PA	Time-varying PA	1994-95 (Tromsø 4); 2001 (Tromsø 5); 2007-08 (Tromsø 6)	All-cause [5263; 33019]*	Mean 18.8 years from 1994 to Dec 2015	Cox regression with time-varying covariates	Baseline: age and sex. Time-dependent: comorbidities, mental health symptoms and CVD risk factors, self-reported health	Hazard ratio
Orsini, 2009	Sweden; population-based cohort of Swedish men residing in Vastmanland and Orebro counties; 0% women; 45-79 years	Total PA	lifetime average	1997/1998 (baseline), recalled: age 30, and 50 years	Prostate Cancer [190; 45887]	Up to 10 years from 1998	Cox regression	Age, waist hip ratio, height, diabetes, alcohol, smoking, education, total energy intake, consumption of dairy product, red meat, and parental history of prostate cancer	Hazard ratio
Ostergaard, 2018	Denmark; The Diet, Cancer and Health study; 51% women; mean 61 (50-64) years	Cycling	5-year change or maintenance	1993-1997, 5 years later	All-cause [2942; 28204]	Up to 309,912 person-years from second time point	Cox regression	Age, gender, years of basic school, higher education, PA at work, leisure-time PA, smoking, monounsaturated, polyunsaturated fat, and saturated fat, and coffee intake.	Hazard ratio
Paffenbarger, 1994	United States; Harvard College Alumni Study ; 0% women; 45-84 years	Total PA	11 to 15-year change or maintenance	1962/1966, 1977	All-cause [2343; 14786]	12 years from 1977	Poisson regression	Age, smoking, hypertension, overweight for height, alcohol, early parental death, and chronic diseases	Rate ratio
Petersen, 2012	Denmark; The Copenhagen City Heart Study; 57% women; 20-93 years	Leisure-time PA	5-year change or maintenance	1976-1978, 1981-1983	All-cause [6494; 10443]	Up to 37 years from 1981-1983 to 2008	Cox regression	Age, education, smoking habits, alcohol consumption, BMI, diabetes, cholesterol and BP lowering therapy in 1981-1983	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Reinikainen, 2015	Finland; The Finnish cohorts of the Seven Countries Study; 0% women; 40-59 years	Occupational PA	10-year time-varying exposure	At least 2 from: 1959 (baseline), 1964, 1969	CVD [850; 1540]	Median 23.1 years from 1959	Cox regression with time-varying covariates	SBP, cholesterol, heart rate, smoking	Hazard ratio
Saint-Maurice, 2019	United States; The NIH-AARP Diet and Health Study; 42% women; 42% women; 50-71 years	Leisure-time PA	adulthood trajectory categorised using GBTM	Recalled: age 15-18, 19-29, 35-39, 40-61 years (10 years before baseline in 1995-1996)	All-cause [71377; 315059] CVD [22219; 315059] Cancer [16388; 315059]	Mean 13.6 years, from 1995-1996	Cox regression	Age, sex, education, race, smoking, energy intake, diet percent fat, alcohol, consumption of red meat, fruit, and vegetable, vitamin/mineral supplementation, and BMI at age 18 years	Hazard ratio
Sanchez-Sanchez, 2020	Spain; Toledo Study of Healthy Aging; 58% women; mean age 75 years	Total PA	4-year trajectories categorised using GBTM	2006-2009; 2011-2013	All-cause [not stated; 1679]	Mean 5.9 years from 2011-2013	Cox regression	Age, gender, Charlson Index, Mini-Mental State Examination, educational level, smoking status, Katz Index, and polypharmacy	Hazard ratio
Schnohr, 2017	Denmark; The Copenhagen City Heart Study; 56% women; 20-98 years	Leisure-time PA	5 to 27-year persistence	At least 2 from: 1976-1978, 1981-1983, 1991-1994, 2001-2003	All-cause [7841; 12314] CHD [1089; 12314]	Up to 33 years (all-cause), and up to 31 years (CHD) from second examination	Cox regression with time-varying covariates	Age, sex, smoking, education, income, drinking habits, diabetes, examination number and incident CHD and cancer admissions during follow-up	Hazard ratio
Shaw, 2014	Sweden; the level of living survey (LNU) and the Swedish panel study of living conditions of the oldest old (SWEOLD); 51% women; mean 44 years	Total PA	13-year change or maintenance	1968, 1981	All-cause [875; 1682]	Up to 26 years from 1981	Cox regression	Age, sex, education, social class, and health problems (circulatory, mobility, and psychological) in 1981	Hazard ratio
Sheehy, 2020	United States; The Black Women's Health Study; 100% women; 21-69 years	Leisure-time PA (walking)	20-year time-varying exposure	1995, 1997, 1999, 2001, 2009, 2011, 2015	All-cause [4719; 52,993] CVD [1697; 52,993] Cancer [1256; 52,993]	22 years from 1995	Cox regression with time-varying covariates	Age, calendar year, neighbourhood SES, education, BMI, smoking, alcohol consumption, diet quality, hypertension, and diabetes.	Hazard ratio
Sherman, 1999	United States; Framingham Heart Study; 59% women; 38-70 years	Total PA	distant and recent exposure	1956-1958, 1969-1973	All-cause [NA; 2372] CVD [NA; 2372]	16 years from 1969-1973	Cox regression	Age, BP, Metropolitan relative weight, cholesterol, smoking, glucose intolerance, left ventricular hypertrophy COPD, or cancer (excluding melanoma skin cancer)	Hazard ratio
Shortreed, 2013	United States; Framingham Heart Study; 57% women; 38-68 years	Total PA	adulthood exposure	1956, 1970/1972, 1986/1988	All-cause [3521; 4729] CVD [1313; 4729]	40 years from 1956 to 1996	Marginal structural model	Baseline covariates (age, sex, education, job type, birth country, weight at 25 years, height) and covariates at follow-up visits: BMI, smoking, marital status, alcohol, blood glucose and diagnosis of a chronic disease (diabetes or cancer) or comorbid condition (arthritis, left ventricular hypertrophy, ankle oedema, pulmonary disease)	Rate ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Stenholm, 2015	Italy; InCHIANTI study; 56% women; 65+ years	Total PA	Adulthood cumulative exposure	Ages 20-40 years and 40-60 years (recalled), 1998 (interviewed)	All-cause [471;1149]	10 years from 1998	Cox regression	Age, sex, and education, smoking, BMI, alcohol consumption.	Hazard ratio
Stensvold, 2020	Norway; Generation 100 (RCT); 50% women; mean age 72.8 years	PA interventions	5-year intervention Intervention 1: 3d/wk 30mins MPA and 2d/wk HIIT sessions; Intervention 2: 3d/wk 30mins MPA and 2d/wk MICT sessions	Supervised sessions every sixth week. Control: asked to perform 30mins of MPA 5d/wk;	All-cause [72; 1567]	5 years from randomisation	Cox regression	Stratification variables: sex, cohabitation status and age at study entry	Hazard ratio
Stessman, 2009	Israel; Jerusalem Longitudinal Cohort Study; 43% women; 70 years	Total PA	15-year time-varying exposure	Age 70,78, 85 years	All-cause [512; 1861]	18 years, from age 70	Cox regression with time-varying covariates	Age (all participants started at 70), sex, financial status, origin, BMI, smoking, ease of performance in ADLs, hypertension, ischemic heart disease, diabetes, history of neoplasm, and renal disease	Hazard ratio
Talbot, 2007	United States; Baltimore Longitudinal Study of Aging; 37% women; 19 to 90+ years	Leisure-time PA	1) 38-year time-varying exposure in men; 2) 18-year time-varying exposure in women	1) 2-year intervals from 1958 to 1996 for men; 2) 2-year intervals from 1978 to 1996 for women	All-cause [1) 538; 2) 90; 1) 1316; 2) 776]	1) Mean of 21 years for men; 2) mean 10 years for women from baseline	Cox regression; mixed-effect model	Stratified by age and sex, adjusted for cholesterol, BMI, smoking, and hypertension	Hazard ratio
Wannamethee, 1998	United Kingdom; The British Regional Heart Study; 0% women; 40-59 years	Leisure-time PA	12 to 14-year change or maintenance	1978-80, 1992	All-cause [217; 4260] CVD [92; 4260]	4 years (all-cause) and 3 years (CVD) from 1992	Cox regression	Age, smoking, social class, BMI, and self-perception of health	Hazard ratio
Williamson, 2019	Australia; The Melbourne Collaborative Cohort Study; 63% women; 40-69 years	Total PA	1) 8-year hypothetical intervention; 2) 8-year time-varying exposure	1990-1994 (T0), 1995-1999 (T1), 2003-2007 (T2)	All-cause [2163; 18386]	Median 13.6 years, from 1995–1999	1) The parametric g-formula; 2) Cox regression with time-varying covariates	T0: sex, ethnicity, education, alcohol, BP, cholesterol, family history of heart attack; T1: age, BMI, smoking, living alone, history of angina, arthritis and asthma; T2: Living alone, BMI, smoking, cholesterol	Risk ratio and risk difference
Wolin, 2010	United States; Cancer Prevention Study (CPS) II Nutrition Cohort; 53% women; 40-92 years	Leisure-time PA	1) 10-year and 2) 15-year change or maintenance	1) 1982, 1992; 2) 1982, 1997	Colon Cancer [1) 846; 2) 602; 158253]	1) up to 14 years from 1992 to 2006; 2) 9 years from 1997 to 2006	Cox regression	1) Sex, education, smoking, use of postmenopausal hormones (among women only), multivitamin intake, red meat, folate, alcohol, NSAIDs, fibre, calcium, total energy, and BMI; 2) covariates in 1) and screening history	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Xue, 2012	United States; Women's Health and Aging Study (WHAS) II; 100% women; 70-79 years	Leisure-time PA	12-year trajectory	1994 (baseline) and 6 follow-up visits, each about 18 months apart	All-cause [149; 433]	Median 12 years between 1994 and 2009	Cox regression; latent class analysis model	Age, race, educational level, and NHIS activity status at baseline	Hazard ratio
Yang, 2020	Australia; The Australian Diabetes, Obesity and Lifestyle Study (AusDiab); 55%; mean age 56.5 years in 2004-2005	Leisure-time PA and TV viewing	7-year sustained PA based on guidelines	1999-2000 (pre-baseline); 2004-2005 (baseline); 2011-2012	All-cause [781; 6377]	Mean 13 years from 2004-2005	Parametric g-formula	Time-fixed: sex, baseline age, quintiles of an area-based index of relative socioeconomic advantage and disadvantage, country of birth, and level of education. Time-varying: self-reported history of high cholesterol, high blood pressure, heart disease, and diabetes, and self-reported general health status; waist circumference, Mediterranean diet score, smoking status, and alcohol intake.	Risk ratio and risk difference
Yoneda, 2020	14 longitudinal studies that are publicly available or are affiliated with the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) network; 47% to 71% women; mean ages 70 to 82 years	PA, type varies across studies	Time-varying PA	Studies with at least six waves.	All cause [9280;52039]	Varies across studies	Multistate survival analysis by study; Random effects meta-analysis to combine	Baseline age, sex, education, and chronic conditions (unstated)	Hazard ratio
Studies examining sedentary behaviour									
Yang et al, 2020 examined both Leisure-time PA and TV viewing. Its study characteristics are presented under "Studies examining physical activity".									
Cabanas-Sanchez, 2018	Spain; No information; 57% women; ≥ 60 years	Sitting time	2-year change or maintenance	2001, 2003	CVD [409; 2657]	Mean 9.2 years from 2003	Cox regression	Age, sex, education, smoking, alcohol, BMI, perceived health, limitations in mobility, limitations in agility, and the number of the following diseases: chronic lung disease, heart disease, diabetes, osteomuscular disease, and cancer	Hazard ratio
Grunseit, 2017	Norway; Nord-Trøndelag health study (HUNT); 53% women; ≥ 19 years	Sitting time	11-year change or maintenance	1995-1997, 2006-2008	All-cause [1212; 25651] CHD [388; 25651]	Mean 6.2 years from 2006-2008	Cox regression	Age, sex, baseline measures of education, PA, smoking, BMI, general health and self-reported diagnosis of cardio-metabolic disease	Hazard ratio
Keadle, 2015	United States; NIH-AARP Diet and Health Study; 40% women; 50-71 years	TV viewing	10-year change or maintenance	1994-1996, 2004-2006	All-cause [20104; 165087]	Up to 8 years, from 2004-2006	Cox regression	Age, sex, race, education, smoking, heart disease, other chronic conditions, depression, health status, depression, and change in BMI and moderate to vigorous PA	Hazard ratio

Table 3-1. Summary of study characteristics included in the systematic review (continued)

Author, year	Study population	Exposure type	Exposure categorisation	Time points	Mortality outcome [n deaths; n participants]	Follow-up period	Analysis method	Covariates included in statistical models	Effect measure reported
Lee, 2015	United States; Women's Health Initiative (WHI); 100% women; 50–79 years	Sitting time	6-year change or maintenance	1993-1998 (baseline), 6-year follow-up	All-cause [1855; 77801] CVD [493; 77801] Cancer [736; 77801]	Mean 5.1 years from 6-year follow-up	Cox regression	Age, current weight, education, employment status, ethnicity, PA, smoking status, recent alcohol consumption, new treatment for diabetes, new onset of congestive heart failure and/or angina and incidence of at least one fracture, or broken bone of the hip, foot, pelvis, knee, upper leg, lower leg or tailbone and all at follow-up	Hazard ratio
Leon-Munoz, 2013	Spain; A cohort study of the non-institutionalised Spanish population; 57% women; ≥ 60 years	Sitting time	2-year change or maintenance	2001, 2003	All-cause [846; 2635]	8-9 years, from 2003 to 2011	Cox regression	Sex, age, education, smoking, alcohol, BMI, PA, ischemic heart disease, stroke, diabetes mellitus, osteomuscular disease, cancer, SF-36 physical summary, limitations in mobility, and limitations in agility	Hazard ratio
van der Ploeg, 2015	Denmark; Danish Work Environment Cohort Study (DWECS); % women; 18-59 years	Occupational sitting time	15-year time-varying exposure	2000, 2005	All-cause [533; 8769]	Up to 10 years from 2001 to 2010	Poisson regression with time-varying exposure	Age, gender, socio-economic status, BMI, smoking, leisure time PA and fruit and vegetable consumption	Hazard ratio

ADLs: activities of daily living; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; FEV1: forced expiratory volume in one second; GBTM: group-based trajectory models; GEE: generalised estimating equations; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; NHIS: National Health Interview Survey; PA: physical activity; SBP: systolic blood pressure; SD: standard deviation; SF36: 36-item short form survey.

Table 3-2. Summary of risk of bias assessment for each study included in the systematic review

Table 2. Summary of Risk of Bias Assessment for Each Study Included in the Systematic Review								
First author, year	Risk of bias due to							Overall
	Confounding	Selection of participants	Classification of exposure	Departures from baseline exposures	Missing data	Outcome measurement	Selection of the reported result	
Studies examining physical activity								
Aggio, 2020	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Andersen, 2004	Moderate	Serious	Moderate	Low	NI	Low	Low	Serious
Balboa-Castillo, 2011	Moderate	Moderate	Critical	Moderate	Low	Low	Low	Critical
Bauman, 2017	Critical	Serious	Serious	Moderate	Moderate	Low	Low	Critical
Bembom, 2009	Low	Low	Serious	Low	Low	Low	Low	Serious
Bijnen, 1999	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Byberg, 2009	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Emberson, 2005	Critical	Serious	Serious	Moderate	NI	Low	Low	Critical
Gregg, 2003	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Hein, 1994	Critical	Serious	Serious	Moderate	Low	Low	Low	Critical
Hamer, 2014	Moderate	Low	Moderate	Low	NI	Low	Low	Moderate
Higuera-Fresnillo, 2017	Moderate	Moderate	Critical	Moderate	Low	Low	Low	Critical
Hirvensalo, 2000	Moderate	Low	Moderate	Moderate	Low	Low	Low	Moderate
Holme, 2015	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Hsu, 2018	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Huang, 2020	Serious	Serious	Moderate	Moderate	NI	Low	Low	Serious
Huerta, 2016	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Hulsegge, 2016	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Jasiukaitiene, 2021	Moderate	Serious	Moderate	Moderate	NI	Low	Low	Serious
Johansson, 1999	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Joseph, 2020	Moderate	Low	Critical	Low	NI	Low	Low	Critical
Kaplan, 1996	Serious	Low	Moderate	Low	NI	Low	Low	Serious
Karvinen, 2015	Moderate	Serious	Moderate	Moderate	Moderate	Low	Low	Serious

Table 3-2. Summary of risk of bias assessment for each study included in the systematic review (continued)

First author, year	Risk of bias due to							Overall
	Confounding	Selection of participants	Classification of exposure	Departures from baseline exposures	Missing data	Outcome measurement	Selection of the reported result	
Laddu, 2018	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Lantz, 2010	Moderate	Low	Serious	Low	Moderate	Low	Low	Serious
Lee, 2003	Serious	Low	Moderate	Low	Low	Low	Low	Serious
Lee, 2004	Serious	Low	Moderate	Low	Low	Low	Low	Serious
Lee, 2014	Moderate	Serious	Moderate	Moderate	NI	Low	Low	Serious
Lewis, 2018	Moderate	Serious	Moderate	Moderate	Moderate	Low	Low	Serious
Lissner, 1996	Serious	Serious	Critical	Low	NI	Low	Low	Critical
Moholdt, 2020	Moderate	Serious	Moderate	Moderate	Moderate	Low	Low	Serious
Mok, 2019	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Myers, 2004	Critical	Serious	Moderate	Moderate	Low	Low	Low	Critical
Newman, 2016	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate
Nordstoga, 2019	Moderate	Serious	Critical	Moderate	Moderate	Low	Low	Critical
Opdal, 2020	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Orsini, 2009	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Ostergaard, 2018	Moderate	Serious	Moderate	Moderate	Moderate	Low	Low	Serious
Paffenbarger, 1994	Serious	Serious	Moderate	Moderate	NI	Low	Low	Serious
Petersen, 2012	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Reinikainen, 2015	Serious	Serious	Serious	Low	Moderate	Low	Low	Serious
Saint-Maurice, 2019	Moderate	Serious	Serious	Moderate	NI	Low	Low	Serious
Sanchez-Sanchez, 2020	Moderate	Serious	Moderate	Moderate	Moderate	Low	Low	Serious
Schnohr, 2017	Moderate	Serious	Moderate	Low	NI	Low	Low	Serious
Shaw, 2014	Serious	Serious	Serious	Moderate	NI	Low	Low	Serious
Sheehy, 2020	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Sherman, 1999	Serious	Low	Moderate	Moderate	Low	Low	Low	Serious

Table 3-2. Summary of risk of bias assessment for each study included in the systematic review (continued)

First author, year	Risk of bias due to							Overall
	Confounding	Selection of participants	Classification of exposure	Departures from baseline exposures	Missing data	Outcome measurement	Selection of the reported result	
Shortreed, 2013	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Stenholm, 2015	Moderate	Serious	Serious	Moderate	Moderate	Low	Low	Serious
Stensvold, 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Stessman, 2009	Moderate	Low	Critical	Low	NI	Low	Low	Critical
Talbot, 2007	Serious	NI	Moderate	Moderate	NI	Low	Low	Serious
Wannamethee, 1998	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Williamson, 2019	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Wolin, 2010	Serious	Serious	Serious	Moderate	Low	Low	Low	Serious
Xue, 2012	Serious	Low	Moderate	Moderate	Low	Low	Low	Serious
Yang, 2020	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Yoneda, 2020	Serious	Serious	NI	Low	NI	Low	Low	Serious
Studies examining sedentary behaviour								
Cabanas-Sanchez, 2018	Moderate	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Grunseit, 2017	Serious	Serious	Moderate	Moderate	Moderate	Low	Low	Serious
Keadle, 2015	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Lee, 2015	Moderate	Serious	Moderate	Moderate	NI	Low	Low	Serious
Leon-Munoz, 2013	Moderate	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
van der Ploeg, 2015	Moderate	Moderate	Moderate	Low	Moderate	Low	Low	Moderate

NI: no information.

Table 3-3. Relative risks for sedentary behaviour over time in relation to all-cause, cardiovascular, or cancer mortality from the studies included in the systematic review

Exposure category by study (First author, year)	All-cause mortality		CVD mortality		Cancer mortality	
	HR ^a	95% CI	HR ^a	95% CI	HR ^a	95% CI
Cabanas-Sanchez, 2018, sitting						
Consistently high (based on sex-specific medians ^b)			1.00			
Consistently low			0.67	(0.46, 0.96)		
Increased: low to high			1.18	(0.87, 1.59)		
Decreased: high to low			0.77	(0.56, 1.07)		
Grunseit, 2017 ^c, sitting						
Consistently high ≥ 8 h/d	1.00		1.00			
Consistently low < 8 h/d	0.80	(0.67, 0.95)	0.67	(0.50, 0.90)		
Increased from < 8 to ≥ 8 h/d	1.20	(0.94, 1.53)	1.24	(0.82, 1.88)		
Reduced from ≥ 8 h/d to < 8 h/d	0.82	(0.65, 1.04)	0.87	(0.58, 1.30)		
Keadle, 2015, TV viewing						
Consistently high 5+ h/d	1.00					
Consistently low < 3 h/d	0.78	(0.74, 0.82)				
Consistently moderate 3-4 h/d	0.88	(0.83, 0.94)				
Increased from 3 to 3-4 h/d	0.91	(0.85, 0.99)				
Increased from < 3 to 5+ h/d	1.13	(1.02, 1.26)				
Lee, 2015, sitting						
Maintained high ≥ 10 h/d	1.00		1.00		1.00	
Maintained low ≤ 9 h/d	0.49	(0.39, 0.63)	0.76	(0.55, 1.06)	0.52	(0.42, 0.66)
Increased from ≤ 9 to ≥ 10 h/d	0.79	(0.58, 1.07)	1.24	(0.85, 1.81)	0.82	(0.61, 1.09)
Decreased from ≥ 10 to ≤ 9 h/d	0.71	(0.54, 0.95)	0.84	(0.56, 1.26)	0.73	(0.55, 0.97)
Leon-Munoz, 2013, sitting						
Consistently high: $>$ median ^d	1.00					
Consistently low: $\leq$ median ^d	0.75	(0.62, 0.90)				
Increased from $\leq$ median to $>$ median	0.91	(0.76, 1.10)				
Decreased from $>$ median to $\leq$ median	0.86	(0.70, 1.05)				
van der Ploeg, 2015, occupational sitting						
≥ 24 h/w	1.00					
< 24 h/w	0.80	(0.58, 1.11)				
Yang, 2020, TV viewing						
Hypothetical scenario (2+ h/d TV viewing in physically inactive adults)	1.00					
Hypothetical TV viewing intervention (reduce TV viewing to < 2 h/d)	0.85	(0.60, 1.10)				

HR: hazard ratios; CI: confidence intervals; CVD: cardiovascular disease; h/d: hours/day; h/w: hours/week. ^a All studies reported hazard ratios. ^b The median sitting time was 4.00 h/d (men) and 4.29 h/d (women) in 2001, and 4.84 h/d (men) and 5.03 h/d (women) in 2003. ^c The presented estimates for CVD mortality are for cardiometabolic mortality. ^d The median sitting time was not reported.

Chapter 4 Data sources and statistical methods

To address Objectives 2 to 4 of the thesis, I analysed data from three prospective cohort studies in which exposures of interest and other covariates were assessed on multiple occasions: the MCCS, the AusDiab, and the ALSWH 1946-1951 birth cohort. In this chapter, I will give an overview of the three cohort studies and describe the statistical methods used for data analyses.

4.1 Data sources

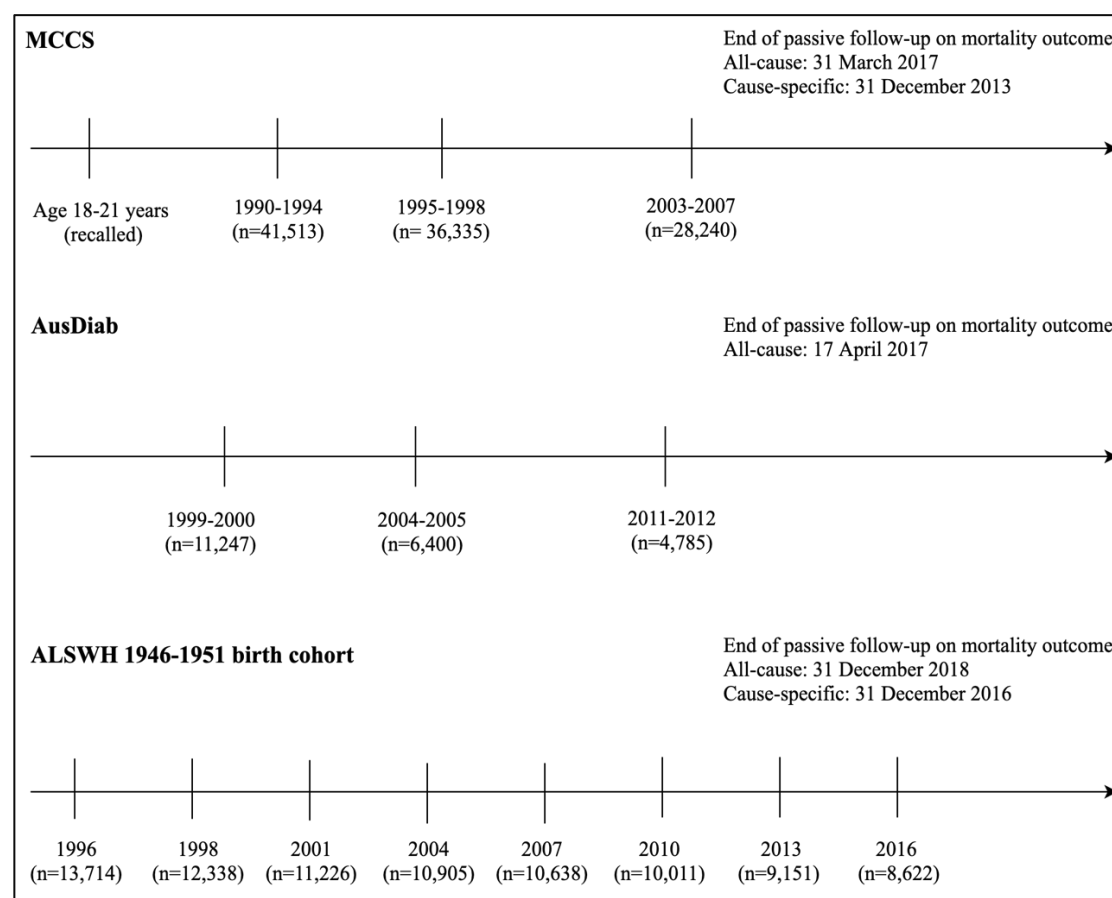
This section outlines the cohort recruitment and data collection of the MCCS, AusDiab, and the ALSWH. An overview of the study profiles of the three cohort studies is presented in Table 4-1, and Figure 4-1 shows the timelines of data collection.

Table 4-1. Profiles of the MCCS, AusDiab, and ALSWH cohort studies

Profiles	MCCS ¹⁹⁰	AusDiab ¹⁹¹	ALSWH 1946-1951 ^{192,193}
Participants recruited	41,513	11,247	13,714
Recruitment period	1990 to 1994	1999 to 2000	1996
Age at baseline	40 to 69 years	25 years and older	45 to 50 years
Percentage of women at baseline	54%	55%	100%
Recruitment area	Metropolitan Melbourne	Australia	Australia
No. of waves of exposure data collected	4	3	8
Exposure of interest	BMI	Physical activity and TV viewing time	Alcohol consumption
Outcome of interest	All-cause, cancer, and CVD mortality	All-cause mortality	All-cause and cancer mortality

MCCS: Melbourne Collaborative Cohort Study; AusDiab: Australian Diabetes, Obesity and Lifestyle Study; ALSWH 1946-1951: Australian Longitudinal Study on Women's Health 1946-1951 birth cohort; BMI: body mass index; CVD: cardiovascular disease.

Figure 4-1 Timelines of the data collection and outcome ascertainment in the MCCA, AusDiab, and ALSWH 1946-1951 birth cohort



MCCA: Melbourne Collaborative Cohort Study; AusDiab: Australian Diabetes, Obesity and Lifestyle Study; ALSWH 1946-1951: Australian Longitudinal Study on Women's Health 1946-1951 birth cohort.

4.1.1 The Melbourne Collaborative Cohort Study

To address Objective 2, I analysed data from the MCCA to investigate the association between adulthood BMI trajectories and mortality. The MCCA, known to participants as Health 2020, was established in the early 1990s to investigate the roles of different lifestyle-related behaviours in the risk of non-communicable diseases.¹⁹⁰ Between 1990 and 1994, the study recruited 41,513 residents of Melbourne Australia with a mean age of 55 years at recruitment (99% aged from 40 to 69 years). Most participants were identified from the Victorian Electoral Enrolment Register and the Melbourne phone directory and were invited by mail. To widen the range of social and lifestyle exposures, southern European migrants were recruited through additional strategies such as announcements via multicultural radio and newspapers, in clubs, churches, and Italian and Greek festivals.

At baseline, data were obtained by physical measurements, and an interviewer-administered questionnaire on demographics, lifestyle and medical conditions. Participants were invited for

the first wave of active follow-up between 1995 and 1998. Of the original participants, 88% (n= 36,335) responded by phone or mail. Physical measurements were not obtained at this wave. Information on lifestyle, medical history and diet were collected by self-administered questionnaire by mail, or interviewer-administered questionnaire by phone. Between 2003 and 2007, participants were invited for the second wave of active follow-up: of the original participants, 68% (n=28,240) attended clinics for data collection. Information on lifestyle, medical history and medication use were collected using self- and interviewer-administered questionnaire at clinics. Physical measurements were also collected at this wave. At baseline and the second wave of active follow-up, diet was measured using self-administered food frequency questionnaires.^{194,195} Participants completed written consent forms. The research protocol was approved by the Cancer Council Victoria's Human Research Ethics Committee.

In the MCCA, BMI data were calculated for four points in time. Body mass was measured at baseline and the second follow-up wave, and self-reported at the first follow-up wave. At baseline, participants were also asked to recall their body mass for age 18 to 21 years. Height was measured at baseline and assumed to be the same at the other waves.

Passive follow-up of the MCCA is on-going. Deaths are ascertained through record linkage to the Victorian Registry of Births, Deaths and Marriages, and the National Death Index (NDI) at the Australian Institute of Health and Welfare. The underlying cause of death was defined according to the International Classification of Diseases codes versions ICD-10. Mortality data used for analyses in this thesis were complete up to 31 March 2017 for all-cause mortality, and up to 31 December 2013 for cause-specific mortality.

4.1.2 The Australian Diabetes, Obesity and Lifestyle Study

To address Objective 3, I analysed data from AusDiab to investigate the effect of physical activity and sedentary behaviour over time on mortality. AusDiab is a population-based cohort study originally established to provide data for understanding diabetes and its risk factors.¹⁹¹ Non-institutionalised adults aged at least 25 years were recruited between 1999 and 2000 in the six states and the Northern Territory of Australia. Within each state and territory, residents of randomly selected census collector districts (i.e., the smallest geographic unit defined by the Australian Bureau of Statistics) were notified through local media advertisements and letters informing them about the study and that interviewers would visit for a household interview.¹⁹¹ Participants provided written informed consent. The study was approved by the Ethics Committee of the International Diabetes Institute.

All household members aged 25 years and over were invited for a biomedical examination at the end of the household interview. Of the eligible individuals who participated in the household interview (n=20,293), 55% (n=11,247) attended the biomedical examination. At the biomedical examination, respondents also completed a self-administered dietary questionnaire¹⁹⁴ and interviewer-administered questionnaires covering demographic characteristics, health and lifestyle-related factors. Participants were invited for two active follow-up waves (between 2004 and 2005, and between 2011 and 2012, respectively). Each wave involved an initial household interview, followed by a biomedical examination and administration of questionnaires. Of the baseline respondents, 57% (n=6,400) participated in the first follow-up wave and 43% (n=4,785) in the second.

Information on weekly physical activity and daily TV viewing hours were collected at all three waves of data collection. Participants' physical activity in the past week was collected using the Active Australia Survey¹⁹⁶; TV viewing time was asked in an interviewer-administered questionnaire.

Vital status and date of death were determined by linkage to the Australian NDI. Mortality data used in this thesis were complete up to 17 April 2017. Only all-cause mortality was examined because numbers of cause-specific deaths were limited.

4.1.3 The Australian Longitudinal Study on Women's Health 1946-1951 birth cohort

To address Objective 4, I used data from the ALSWH to investigate the effect of alcohol consumption over time on mortality. The ALSWH is a population-based prospective cohort study examining the health of three nationally representative cohorts of Australian women born in 1921-1926, 1946-1951, and 1973-1978, respectively. The data used in this thesis are from the 1946-1951 birth cohort. In 1996, participants were randomly selected from women born between 1946 and 1951 and registered in the Australian national health insurance scheme enrolment database, Medicare. Participants completed consent forms. The study protocol was approved by the Human Research Ethics Committees of the University of Queensland and the University of Newcastle.^{192,193}

An estimated 53-56% of invited women completed a questionnaire about their lifestyle and health (n=13,714) in 1996. Further waves of data collection occurred every two to three years: in 1998 (n=12,338), 2001 (n=11,226), 2004 (n=10,905), 2007 (n=10,638), 2010 (n=10,011), 2013 (n=9,151) and 2016 (n=8,622), respectively. Data were collected using paper-based questionnaires via mail, or web-based questionnaires. In this thesis, the first active follow-up

wave in 1998 was used as the baseline to allow adjustment for pre-baseline confounders (measured in 1996) in the analyses. Data from subsequent waves to 2016 were used (Figure 4-1)

Frequency and quantity of alcohol consumption were asked in the self-administered questionnaires at all waves except 2001. Daily alcohol intake (in grams of pure alcohol) was calculated based on the following formula:

$$\text{Alcohol intake (g/day)} = F \times Q \times 10 \div 7,$$

where F is the weekly frequency of alcohol consumption (days/week), and Q is the number of standard drinks on a day of drinking. In Australia, one standard drink contains 10 grams of alcohol.¹⁹⁷ The weekly number of standard drinks is multiplied by 10 and is then averaged over 7 days per week. The ALSWH questionnaire responses and approximate frequency (F) and quantity (Q) are presented in

Table 4-2. A serving of alcoholic beverage can be larger than a standard drink, depending on the type of beverage consumed (Table 4-3). However, the beverage type was not asked in the ALSWH questionnaire. The number of standard drinks in each reported drink can only be approximated. The most consumed alcohol types by Australian women during the ALSWH study period were wine and beer.¹⁹⁸ For this thesis, 1.5 standard drinks were assigned to each reported drink.

Table 4-2 Frequency and quantity of alcohol consumption approximated for each questionnaire response

Question: How often do you usually drink alcoholic beverages?		Question: On a day when you drink alcoholic beverages, how many drinks do you usually have?		
Response	F (days/week) *	Response	Approximate drinks*	Q (Numbers of standard drink/day)^
Never or former	0	I don't drink	0	0
I rarely drink	0.25	1 or 2 drinks	1.5	2.25
<1 /week	0.5	3 or 4 drinks	3.5	5.25
1 or 2 days/week	1.5	5 to 8 drinks	6.5	9.75
3 or 4 days	3.5	≥ 9 drinks	9	13.5
5 or 6 days	5.5			
Every day	7			

F: Weekly frequency; Q: standard drinks on a day of drinking. * For responses reporting a range, the mid-point is used as a multiplying factor ¹⁹⁹. ^ 1 reported drink ≈ 1.5 Australian standard drink

Table 4-3. Numbers of standard drinks in a serving of common alcoholic beverages in Australia

Alcoholic beverages	Australian standard drinks¹⁹⁷
Full strength beer (4.8%), 375ml	1.4 standard drinks
A typical serving of red wine served in restaurants (13.5%), 150ml	1.6 standard drinks
A typical serving of white wine served in restaurants (11.5%), 150ml	1.4 standard drinks
A typical serving of champagne served in restaurants (12%), 150ml	1.4 standard drinks
Full strength ready-to-drink spirits (5.0%), 330ml	1.2 standard drinks

In 2001 and 2013, individuals also completed a separate food frequency questionnaire (FFQ),¹⁹⁵ which included questions about consumption of specific alcoholic beverage types. The amount of each alcoholic beverage (beer, wine, spirits) derived was multiplied by the daily equivalent frequency and estimated alcohol content to calculate the daily alcohol intake.

As the 2001 questionnaire did not include questions on frequency and quantity of alcohol consumption, I calibrated the daily intake calculated from the FFQ using regression calibration²⁰⁰ based on the 2013 survey, where alcohol questions were asked in both the main questionnaire and the FFQ. For alcohol drinkers in 2001:

$$\text{Alcohol intake} = \alpha + \beta \times \text{FFQ intake},$$

where α and β were estimated from linear regression of the questionnaire-estimated intake against FFQ-estimated intake in 2013.

Only all-cause and cancer mortality were examined in this cohort because numbers of deaths from other causes were limited. Deaths were ascertained through record linkage to the NDI at the Australian Institute of Health and Welfare. The underlying cause of death was defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10, codes C00-C97 for cancer deaths). All-cause mortality data were complete to 31 December 2018; data on cause of death were complete to 31 December 2016.

4.2 Statistical analysis: group-based trajectory model

I used a group-based trajectory model to analyse data from the MCCS. The model is an application of finite mixture modelling which is designed to identify distinct clusters of individuals within a population who follow a similar pattern of exposure trajectory over time.^{47,60} It fits longitudinal exposure data by maximum likelihood method as a mixture of two or more latent trajectories with a polynomial function of age. The model selection is often guided by using the Bayesian Information Criterion (BIC) and the log Bayes factor through a two-stage approach recommended by Nagin.²⁰¹ First, for an assumed function of age, models with different numbers of trajectories are compared sequentially by reducing the number of trajectory groups. The model with the best fit is often selected. Next, the selected model is compared against models with other polynomial function of age to determine the shape of each trajectory. Adequacy of the final model can be assessed using various diagnostic measures: the average posterior probability of assignment for each group of 0.7 or higher; odds of correct classification of 5.0 or higher; the proportion of a sample assigned to a certain group close to the proportion estimated from the model; and a reasonably narrow confidence interval around each trajectory (15). After obtaining BMI trajectories in the MCCS using group-based trajectory model, Cox regression was used to estimate HR and 95% CIs for the trajectories.

4.3 Statistical analysis: the parametric g-formula

I used the parametric g-formula to analyse the data from the AusDiab and the ALSWH studies, which depends on the counterfactual definition of causation. In this section, I will first give an overview of causal inference based on counterfactuals. The counterfactual notations used in this section are based on the work by Miguel Hernán and James Robins.^{202,203} I will then describe the challenges in estimating the effects of time-varying exposures, and how the parametric g-formula addresses them.

4.3.1 Causal inference based on counterfactuals

Causal inference forms a fundamental part of epidemiology to uncover the causes of diseases, which is particularly important when studying modifiable risk factors for health outcomes. This is because presence of a causal relationship between the exposure and the outcome often indicates the possibility for public health intervention.²⁰⁴

The counterfactual reasoning of causation implies a contrast between the outcome when the exposure had occurred and the outcome when the exposure had not occurred, while everything

else remains the same. If the two outcomes differ, the exposure has a causal effect on the outcome. However, individual causal effects are never identifiable. An individual could only be exposed or unexposed at a given time; hence only one of the two potential outcomes could be observed. The unobserved one is the counterfactual outcome (i.e., the outcome is contrary to fact). Consider a binary exposure variable A (0 for unexposed, 1 for exposed) and a binary outcome variable Y (0 for alive, 1 for dead). The presence of a causal effect of A on Y for an individual can be defined as $Y^{a=1} \neq Y^{a=0}$, where $Y^{a=1}$ is the outcome that would have been observed had the individual been exposed, and $Y^{a=0}$ is the outcome that would have been observed had the individual been unexposed.²⁰²

While individual causal effects are generally not identifiable, average causal effects in a population can be estimated. The presence of an average causal effect of exposure A on a binary outcome Y can be defined as $\Pr[Y^{a=1}=1] \neq \Pr[Y^{a=0}=1]$, where $\Pr[Y^{a=1}=1]$ is the proportion of individuals that would have died had all individuals in the population been exposed, and $\Pr[Y^{a=0}=1]$ is the proportion of individuals that would have died had all individuals been unexposed. This definition can be expressed as $E[Y^{a=1}] \neq E[Y^{a=0}]$ to represent both binary and non-binary outcomes, where the letter E stands for expectation and is often used to represent the population average or mean. An ideal randomised controlled trial (i.e., no loss to follow-up or non-adherence) is often regarded as a ‘gold standard’ for causal inference because it establishes exchangeable groups through randomisation (i.e., the groups would have the same risk of death if assigned to the same intervention). In an ideal randomised controlled trial examining the effect of A on Y , both of the two potential population average outcomes, $E[Y^{a=1}]$ and $E[Y^{a=0}]$, could be estimated in two exchangeable groups of individuals randomly assigned to receive $A=0$ or $A=1$. The average causal effect of A can be estimated by computing $E[Y^{a=1}] - E[Y^{a=0}]$, where $E[Y^{a=1}]$ is observed in the intervention group, and $E[Y^{a=0}]$ is observed in the control group.

In observational studies, causal effects are not as immediately identifiable as in ideal randomised controlled trials. A set of assumptions need to be made for estimating the causal effect using observational data: (1) conditional exchangeability, which requires the exposed and the non-exposed group to be exchangeable (i.e., the exposed and the unexposed groups would have the same risk of death if under the same exposure level) conditional on a set of potential confounders; (2) positivity, that is, a positive probability of being exposed for all levels of the confounders; and (3) consistency, which means that the observed outcome for every individual equals the potential outcome if they had been assigned that exposure.²⁰²

4.3.2 Estimating the effects of time-varying exposures

To estimate the effect of an exposure on the outcome in an observational study where randomisation is absent, it is important to consider the role of confounding variables, i.e., the observed effect may be due to common causes of the exposure and the outcome rather than to a true effect.¹⁶ As described in the previous section (4.3.1), valid causal inference requires conditional exchangeability, which can be achieved through adjusting for potential confounders. Valid causal inference with time-varying exposures requires adjusting for all confounders, time-fixed and time-varying, to achieve conditional exchangeability at each time point. This is referred to as sequential conditional exchangeability.

Figure 4-2 illustrates three scenarios in which confounding is present using causal diagrams. A causal diagram (also known as causal directed acyclic graph, DAG) is a representation of assumptions of the underlying causal relationships relevant to the research question. Nodes in causal diagrams present variables, and arrows indicate the presence of a causal effect and its direction.²⁰⁵

Figure 4-2a depicts the relationship between a binary exposure A at time 0 (A_0), outcome (Y), and a set of variables (L_0) that is sufficient for confounding adjustment to achieve conditional exchangeability in a time-fixed setting. Stratification-based methods such as restriction and matching can be used to remove confounding through estimating the association between A_0 and Y in subsets defined by L_0 . The most widely used method is to include all variables in L_0 in a regression model. This is also a form of stratification that pools associations between A_0 and Y estimated within levels of all variables in A_0 .

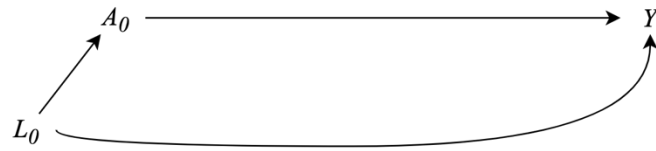
Figure 4-2b illustrates a longitudinal setting, where the exposure A varies over T time points (from A_0 to A_T). In this setting, confounders are not affected by prior exposure. Including L_0 - L_T also adjusts for confounding appropriately by blocking the spurious effects transmitting from exposure to outcome through L_0 - L_T .

Figure 4-2c shows a more complex longitudinal setting where confounders are affected by prior exposure. In this scenario, stratification-based methods are no longer suitable for confounding adjustment. This is because L_1 to L_T lie on several causal pathways from A_0 - A_T to Y . Pooling associations between exposure and outcome within the stratum of L_1 to L_T blocks the part of the joint effect of A_0 to A_t on Y that acts through L_1 to L_t .²⁰²

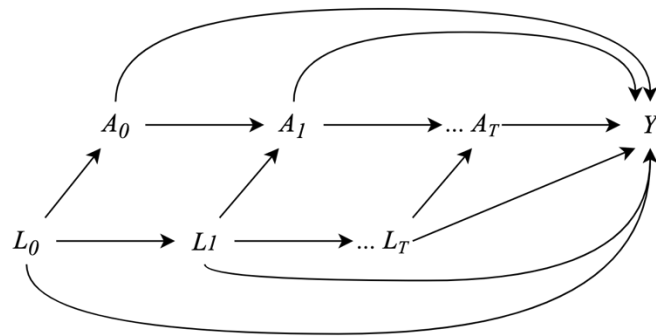
In lifestyle epidemiology, settings presented in Figure 4-2c are common. A time-varying confounder often also lies on causal pathways from exposure to outcome. For example, when estimating the effect of sedentary behaviour on mortality, obese individuals are more likely to be sedentary and have a higher mortality risk (i.e., obesity is a confounder), and sedentary behaviour, in turn, affects obesity status at the next time point (i.e., obesity lies on a causal pathway).²⁰⁶ Conditioning on time-varying obesity status in a regression model adjusts away the effect of sedentary behaviour on mortality mediated through obesity. Therefore, alternative methods of confounding adjustment are required in such settings.

Figure 4-2. Causal diagrams representing the relationships between the exposure A, outcome Y in the presence of (a) time-fixed confounding by L_0 , (b) time-varying confounding by L_0 to L_T , and (c) time-varying confounding affected by prior exposure.

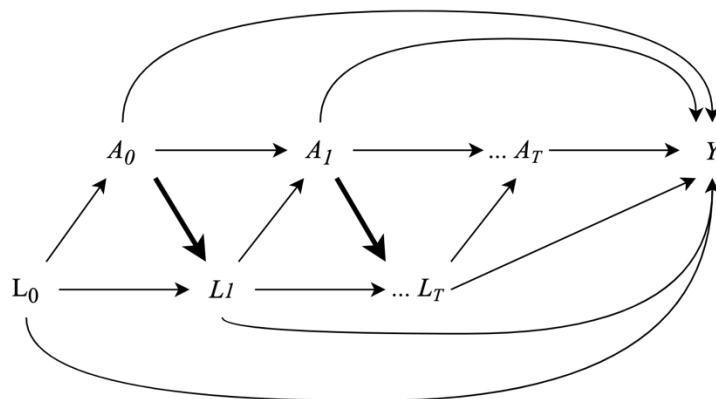
(a) Time-fixed confounding



(b) Time-varying confounding



(c) Time-varying confounding affected by prior exposure



A: exposure; Y: outcome; L: a set of variables that are sufficient for confounding adjustment. Subscripts denote time point.

4.3.3 The parametric g-formula

The g-formula (i.e., generalisation of standardisation, also known as g-computation) was first introduced by Robins in 1986 for time-varying settings.^{187,207} Due to the substantial contribution of Robins and Hernán to both the development and explanation of the methodology, descriptions of the method in this section draw primarily from their recent book on causal inference.²⁰²

Standardisation is a common alternative to stratification-based methods for control of confounding in epidemiology (e.g., age standardisation). In a setting where the effect of a time-fixed exposure A_0 on Y is to be estimated (Figure 4-2a), the expected value of Y under the scenario that everyone has the exposure a_0 can be estimated using standardisation based on the following formula:

$$E(Y^{a_0}) = \sum_{l_0} E[Y|A_0 = a_0, L_0 = l_0] Pr(L_0 = l_0)$$

The $E(Y^{a_0})$ is a weighted average of the mean outcome ($E[Y|A_0 = a_0, L_0 = l_0]$) conditional on the time-fixed exposure and confounders. This weighted average is the g-formula, i.e., the mean outcome standardised to the distribution of all the confounders in L_0 in the study sample. The g-formula generalised to high dimensional time-varying settings is:

$$E(Y^{\bar{a}}) = \sum_{\bar{l}} E[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}] \prod_{t=0}^T f(l_t|\bar{a}_{t-1}, \bar{l}_{t-1}),$$

where the overhead bar denotes history; $E(Y^{\bar{a}})$ is the weighted average of the mean outcome $E[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}]$ conditional on the probability density function of the time-varying exposure and confounders history over T time points $f(l_t|\bar{a}_{t-1}, \bar{l}_{t-1})$. In studies with high dimensional data, components of the g-formula cannot be computed directly but need to be estimated by fitting parametric regression models. The weighted average can be approximated through Monte Carlo simulation. This approach to parametric estimation of the g-formula quantities is referred to as the parametric g-formula.

The parametric g-formula can be implemented in three steps. First, parametric models are fitted to the original data to obtain conditional probabilities of covariates conditional on past exposure and covariate histories. Second, in a Monte Carlo sample, sampled with replacement from the

original data, time-varying exposures, covariates and outcomes are then simulated using the conditional probabilities obtained from the first step for each exposure scenario of interest (for example, always exposed and always unexposed). Finally, effect measures such as risk ratios and risk differences can be calculated, and 95% CIs obtained using non-parametric bootstrapping. The modelling and simulation are carried out by conditioning only on past exposure and confounders; therefore, the parametric g-formula does not introduce bias due to adjustment of intermediate variables on causal pathways. Under the identifiability assumptions of sequential conditional exchangeability and consistency, and the parametric modelling assumptions (i.e., no model misspecification), the g-formula estimates the causal effect of the time-varying exposure on the outcome. Because the parametric g-formula is based on outcome regression, it can be used in the absence of positivity under the assumption that the outcome model is correctly specified to extrapolate beyond the data when positivity fails in some strata of the population.

The parametric g-formula was used to analyse data from AusDiab and the ALSWH 1946-1951 birth cohort, where information on potential confounders were measured at all time points. In the MCCS, participants were asked to recall body mass for age 18 to 21 years. No confounder information was recalled for this age. Therefore, the parametric g-formula was not applied to MCCS data because its causal interpretation requires complete information on the history of all time-varying confounders for the assumption of sequential conditional exchangeability to be plausible.

Chapter 5 Trajectories of body mass index in adulthood in relation to all-cause and cause-specific mortality

Objective 2 of the thesis is to examine BMI trajectories over adulthood and their impact on mortality. To address Objective 2, I analysed data from the MCCS. This chapter presents the authors accepted version of the following paper published in *BMJ Open*:

Yi Yang, Pierre-Antoine Dugué, Brigid M Lynch, Allison M Hodge, Amalia Karahalios, Robert J MacInnis, Roger L Milne, Graham G Giles, Dallas R English. Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study. *BMJ Open* 2019;9:e030078.doi: 10.1136/bmjopen-2019-030078

Supplementary material related to this publication is included in Appendix B.

Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study

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ABSTRACT

Objective Limited research has assessed the association between patterns of body mass index (BMI) change across adulthood and mortality. We aimed to identify groups of individuals who followed specific group-based BMI trajectories across adulthood, using weight collected on three occasions and recalled data from early adulthood, and to examine associations with all-cause and cause-specific mortality.

Design Prospective cohort study.

Setting Melbourne, Australia.

Participants Adults (n=29,881) enrolled in the Melbourne Collaborative Cohort Study, who were aged from 40 to 70 years between 1990 and 1994, and had BMI data for at least three time points.

Outcome Deaths from any cause before 31 March 2017, and deaths from obesity-related cancers, cardiovascular diseases and other causes before 31 December 2013.

Results We identified six group-based BMI trajectories: lower-normal stable (TR1), higher-normal stable (TR2), normal to overweight (TR3), chronic borderline obesity (TR4), normal to class I obesity (TR5), and overweight to class II obesity (TR6). Generally, compared with maintaining lower-normal BMI throughout adulthood, the lowest mortality was experienced by participants who maintained higher-normal BMI (HR=0.90, 0.84 to 0.97); obesity during midlife was associated with higher all-cause mortality even when BMI was normal in early adulthood (HR=1.09, CI 0.98 to 1.21); prolonged borderline obesity from early adulthood was also associated with elevated mortality (HR=1.16, CI 1.01 to 1.33). These associations were stronger for never-smokers and for death due to obesity-related cancers. Being overweight in early adulthood and becoming class II obese was associated with higher CVD mortality relative to maintaining lower-normal BMI (HR=2.27, CI 1.34 to 3.87).

Conclusion Our findings highlight the importance of weight management throughout adulthood to reduce mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Multiple exposure assessments were used to derive trajectories in BMI across adulthood.
- The analytic approach identified specific higher-risk BMI trajectories that would not have been identifiable using the conventional approach of grouping participants into categories of change.
- We did not have information on weight between age 18-21 years and baseline, which limited us from identifying trajectories of how people gained weight between the two time points.

INTRODUCTION

Obesity is associated with increased risk of mortality,^{10-12,27,208} cardiovascular disease (CVD) and several cancers.^{26,38} Most of this evidence is based on anthropometric data collected at one time, typically in participants' mid to late life at recruitment to a cohort. The importance of considering body mass as a time-varying exposure to account for changes over the lifespan has been highlighted.²⁰⁹ Some studies have assessed changes in body mass using pre-defined categories (e.g. weight gain, weight stable, weight loss).^{46,51,210-213} This approach can introduce statistical bias by creating groups that reflect predominantly random variation, and can fail to identify more complex patterns of change.⁴⁷ One study used pictograms to assess body shape throughout life to create body shape trajectories.⁵⁵ Stable lean body shape from age 5 to 50 years had the lowest mortality.⁵⁵ Two studies using body mass index (BMI) found the lowest mortality for individuals consistently overweight during their mid to late life; the highest mortality was for obese individuals who gained weight⁵³ and for thin individuals who lost weight.⁵⁴ As these studies only used data from mid-adulthood onwards, they could not assess the effects of long term versus short term obesity and its potential impact on mortality.

In this study, we used data from the Melbourne Collaborative Cohort Study (MCCS). We have previously reported on mortality in relation to baseline BMI and change in BMI over approximately 12 years.^{213,214} Here, we aimed to identify groups of individuals who followed specific BMI trajectories across adulthood, using weight collected on three occasions and recalled data from early adulthood, and to examine associations with all-cause and cause-specific mortality.

METHODS

Study population

The MCCA is a prospective cohort study of 41,513 residents of Melbourne Australia with a mean age of 55 years at recruitment (99% aged between 40 and 69 years) from 1990-94 (baseline). Southern European migrants were deliberately recruited to widen the range of social and lifestyle exposures. At baseline, data were obtained by physical measurements, a self-administered food frequency questionnaire,¹⁹⁴ and an interviewer-administered questionnaire on demographics, lifestyle and medical conditions. Further waves of data collection occurred from 1995-98 (88% responded by mail or phone) and 2003-07 (68% attended a study centre). Details about the cohort have previously been described.¹⁹⁰ The research protocol was approved by Cancer Council Victoria's Human Research Ethics Committee.

Participant and public involvement

Participants had no involvement in the design of the study. Results are disseminated to participants in annual newsletters.¹⁹⁰

BMI assessment

Weight was recorded for four times (age 18-21 years, years 1990-94, 1995-98, and 2003-07). At baseline, weight was measured following standard protocols²¹⁵ and participants reported their weight at age 18-21 years. Weight was self-reported in 1995-98 and measured in 2003-07. To adjust for measurement error arising from using self-reported weight in 1995-98, a correction was applied to data based on sex- and age-specific comparison of self-reported and measured weight in the Australian National Nutrition Survey.^{216,217} Recalled weight at age 18-21 years was not adjusted, because the correction formula might not be applicable to recalled weight. Height was measured at baseline. BMI was calculated as weight (kg) divided by square of height (m²).

Ascertainment of deaths

Deaths were ascertained through record linkage to the Victorian Registry of Births, Deaths and Marriages, and the National Death Index at the Australian Institute of Health and Welfare. Underlying cause of death was defined according to the International Classification of Diseases codes versions ICD-10. When the cause was unknown, it was classified as "other". Obesity-related cancer deaths were defined as those for which the International Agency for Research on Cancer classified the evidence for causality as sufficient: oesophagus adenocarcinoma,

gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, corpus uteri, ovary, renal cell, meningioma, thyroid, multiple myeloma; or as limited: male breast cancer, fatal prostate cancer, diffuse large B-cell lymphoma.²⁶

Participants selected for this analysis

We excluded participants if they were aged <40 or >70 years at baseline, were underweight (BMI<18.5 kg/m²) at baseline, were diagnosed with cancer before their last BMI measurement, had missing data for any confounding variables, had extreme BMI values at any time (BMI < 15 kg/m² or > 45 kg/m²), or if they had BMI for fewer than three times to allow estimation of potentially non-linear trajectories. These exclusions left 29,881 participants (Supplementary Figure 5-1).

Statistical analysis

BMI trajectories. We used a semiparametric group-based trajectory model^{47,218} to identify latent homogeneity in participants' BMI trajectories from early (age 18-21 years) to late adulthood. The model is an application of finite mixture modelling which assumes the population is composed of a mixture of groups following homogenous developmental courses.⁴⁷ Longitudinal BMI data were fitted as a mixture of several latent trajectories in a censored normal model (allowing for the lower and upper BMI limits) with a polynomial function of age.²¹⁸ We used the Bayesian Information Criterion (BIC) and the log Bayes factor to select optimal shapes and number of trajectory groups through a two-stage approach.⁴⁷ First, the number of groups was determined assuming all trajectory groups were quadratic functions of age. Second, the preferred order of the polynomial (i.e., linear or quadratic) for each trajectory was determined. Participants were assigned to the group for which their posterior predicted probability calculated from the final model was highest. The adequacy of the final model was evaluated using recommended diagnostic measures: average posterior probability of assignment for each group of 0.7 or higher; odds of correct classification of 5.0 or higher; the proportion of a sample assigned to a certain group close to the proportion estimated from the model; and a reasonably narrow confidence interval around each trajectory.⁴⁷

Association of BMI trajectories with mortality. Cox regression with age as the time scale²¹⁹ was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality for each trajectory group. Follow-up began at the date of last BMI assessment and ended at date of death, date when mortality data were complete (31 March 2017 for all-cause mortality, and 31 December 2013 for cause-specific mortality), whichever came first. Models included birth

cohort (< 1930, 1930-39, 1940-49, ≥ 1950), height (continuous in cm), sex (male, female), country of birth (Australia/New Zealand/Northern Europe, Southern Europe), an area-based measure of socioeconomic position (SEIFA) derived from the Australian Census ²²⁰ (quintiles), highest level of education attained (primary school or lower, some high or technical school, completed high or technical school, completed tertiary education), smoking status at last BMI assessment (never, former, current), and these baseline covariates: alcohol drinking status (lifetime abstainer, former, current lower (1-39 g/day for male; 1-19 g/day for female), current higher (≥ 40 g/day for male; ≥ 20 g/day for female)), physical activity score (0, >0 and <4, ≥ 4 and <6, ≥ 6 ; computed from frequency of walking, vigorous and less vigorous exercise over the last 6 months ²²¹), and Mediterranean Diet Score (MDS; 0 to 3, 4 to 6, 7 to 9; detailed calculation is described elsewhere ¹⁹⁵).

Graphical checks based on log-log plots of survival and tests based on Schoenfeld residuals were used to examine the proportional hazards assumption. We stratified the Cox models on covariates that did not satisfy the proportional hazards assumption and fitted interactions between attained age and BMI trajectory for each trajectory that did not meet the assumption. The analyses were repeated after restriction to never smokers at last BMI assessment, because adjustment for smoking status may not be sufficient to control for confounding by smoking.^{10,222,223}

We tested interactions between BMI trajectories and these factors using likelihood ratio tests: sex (male, female), country of birth (Australian/New Zealand/northern Europe, southern Europe), alcohol consumption (lifetime abstainer, former, current lower, current higher), history of diabetes (yes, no), history of heart diseases (yes, no), follow-up duration (<5 years, 5 to <10 years, ≥ 10 years), and baseline age (<60 years, ≥ 60 years).

We repeated the analysis excluding i) the first 2 years of follow-up, and ii) non-respondents for the 2003-07 data collection. Finally, we compared the fit of the models with BMI trajectories and models with last BMI assessment to assess whether trajectory models had better fit than models using the conventional approach based on one BMI assessment. Last BMI measurements were categorised into 6 groups: underweight (BMI < 18.5 kg/m²), lower normal (BMI ≥ 18.5 kg/m² and < 23 kg/m²), higher normal (BMI ≥ 23 kg/m² and < 25 kg/m²), overweight (BMI ≥ 25 kg/m² and < 30 kg/m²), class I obesity (BMI ≥ 30 kg/m² and < 35 kg/m²), and class II obesity (BMI ≥ 35 kg/m²).

Most participants excluded due to insufficient BMI records had baseline and recalled weight at age 18-21 years, but no BMI data in 1995-98 and 2003-07. To see whether selection of participants into the analysis was related to both BMI and death, we compared mean BMI (at age 18-21 years and at baseline) of participants who had three or more records with those who had fewer than three records; we also used unadjusted logistic regression to estimate the odds ratio of death for these two groups.

Statistical analyses were performed using Stata version 14.2 (Stata Corp., College Station, Texas, USA).

RESULTS

The analyses included 29,881 participants (17,475 never-smokers at the latest BMI assessment) (Supplementary Figure 5-1). Six trajectories (TR) of BMI were identified and named according to their shapes in relation to the World Health Organization (WHO) classification of BMI ¹⁹ (Figure 5-1). Almost all participants (94%) had normal BMI at age 18-21 years (TR1, TR2, TR3 and TR5). Two-thirds had an increase in BMI to higher normal (TR2) or overweight (TR3) later in life. A smaller proportion maintained a lower-normal BMI (TR1, 19%) throughout adulthood. Few participants (13%) became obese in midlife (TR5 and TR6) or were consistently borderline obese (TR4; 3%). Model adequacy diagnostics are presented in Supplementary Table 5-1.

The proportion of participants in the highest SEIFA quintile (i.e., most advantaged) and with the highest education decreased across TR1 to TR6 (Table 5-1). Compared with other trajectory groups, participants in the lower-normal stable trajectory (TR1) tended to follow a more Mediterranean diet, be more physically active, and to drink alcohol. Mediterranean diet score, physical activity level and proportion of current alcohol drinkers gradually decreased across TR1 to TR6. A higher proportion of people in the borderline obesity trajectory (TR4) had prevalent heart disease and diabetes at baseline.

Table 5-2 presents HR between trajectories and mortality using stable lower-normal BMI trajectory (TR1) as the reference. All-cause mortality was slightly lower for the stable higher-normal BMI trajectory (TR2, HR=0.90, CI 0.84 to 0.97); trajectories of chronic borderline obesity (TR4) and normal to class I obesity (TR5) had higher all-cause mortality (HR=1.16, CI 1.01 to 1.33, and HR=1.09, CI 0.98 to 1.21, respectively). As the most obese trajectory (TR6) showed evidence of non-proportional hazards, we fitted an interaction between this trajectory

and attained age and presented HRs for age 74, 80 and 85 (25th, 50th and 75th percentiles of age at death). For this trajectory, the HR was greater at younger attained age than at older attained age (from HR=1.31, CI 1.11 to 1.54 for age 74 years, to HR=1.10, CI 0.88 to 1.38 for age 85 years). In never-smokers, while the proportional hazards assumption was not violated, the same pattern (i.e., weaker HRs with increasing age) was seen for TR6. The associations between obesity across adulthood (TR4, TR5, and TR6) and all-cause mortality were stronger than for the whole cohort (HR=1.25, CI 1.02 to 1.53, HR=1.19, CI 1.03 to 1.37, and HR=1.33, CI 1.07 to 1.64, respectively).

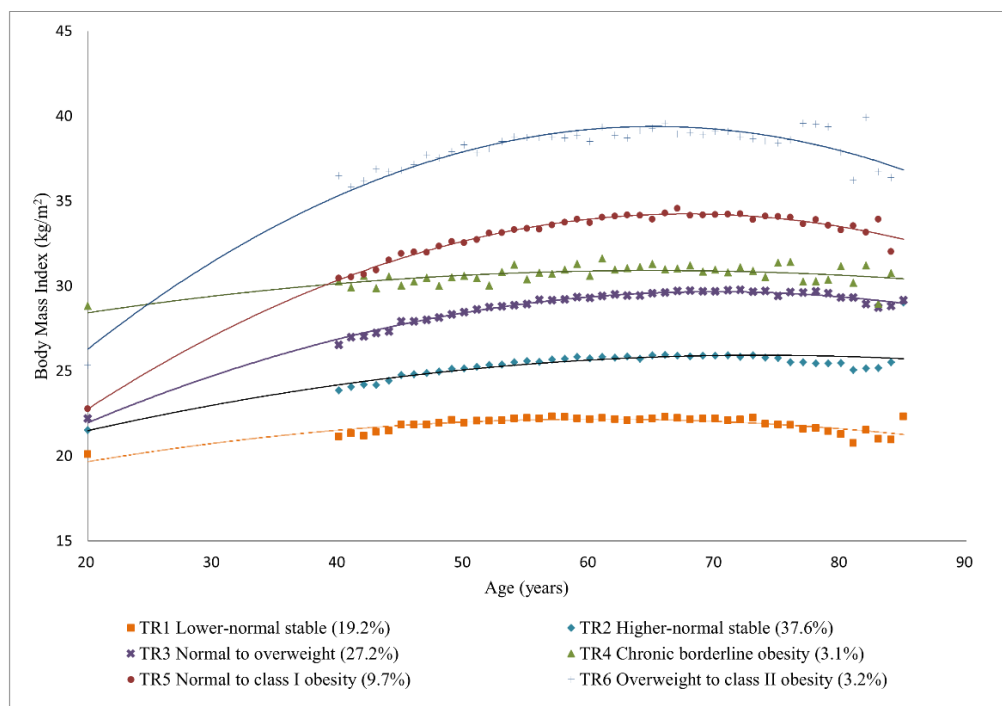
Being obese across adulthood (TR4, TR5, and TR6) showed stronger associations with mortality from obesity-related cancers than with all-cause mortality. Chronic borderline obesity (TR4) was associated with higher risk of death, especially from obesity-related cancers (HR=1.82, CI 1.24 to 2.68 for all participants, and HR=1.92, CI 1.11 to 3.32 for never-smokers). The overweight to class II obesity trajectory (TR6) had increased risk of CVD mortality (HR=2.27, CI 1.34 to 3.87 for the whole cohort; HR=1.62, CI 1.02 to 2.56 for never-smokers). In general, BMI trajectories had weak associations with other-cause mortality (Figure 5-2 and Supplementary Table 5-2).

For the analyses of all-cause mortality, there was no evidence of interaction between BMI trajectory and sex ($p=0.2$), country of birth ($p=0.3$), alcohol consumption ($p=0.7$), history of diabetes ($p=0.2$), history of heart diseases ($p=0.3$), follow-up duration ($p=0.1$), or baseline age ($p=0.2$). HRs were similar after excluding the first 2 years of follow-up (results not shown). After excluding participants who had no 2003-07 data, HRs for cause-specific mortality were generally similar (Supplementary Table 5-3), but with wider confidence intervals; the most obese trajectory (TR6) interacted with attained age overall and in never-smokers for all-cause mortality (Table 5-3).

Models including BMI trajectories fitted slightly better than those with last-measured BMI according to BIC (Supplementary Table 5-4).

Participants with fewer than three BMI records had higher mean BMI at age 18-21 years (22.4 kg/m² and 21.9 kg/m², respectively; $p<0.0001$) and at baseline (28.3 kg/m² and 26.7 kg/m², respectively; $p<0.0001$) than those who had at least three records. They also had higher odds of all-cause mortality (OR=2.06, CI 1.93 to 2.21).

Figure 5-1. BMI trajectories in the Melbourne Collaborative Cohort Study



WHO classification of BMI: underweight (BMI<18.5 kg/m²), normal (BMI≥18.5kg/m² and <25 kg/m²), overweight (BMI≥25 kg/m² and <30 kg/m²), class I obesity (BMI≥30 kg/m² and <35 kg/m²), class II obesity (BMI≥35 kg/m² and <40 kg/m²)

Table 5-1. Characteristics of participants by BMI trajectory groups in the Melbourne Collaborative Cohort Study

	BMI Trajectory Groups					
	TR1 Lower-normal stable	TR2 Higher-normal stable	TR3 Normal to overweight	TR4 Chronic borderline obesity	TR5 Normal to class I obesity	TR6 Overweight to class II obesity
	N=5 748	N=11 229	N=8 130	N=933	N=2 893	N=948
Baseline age, mean(SD)	54.3 (8.9)	55.3 (8.7)	54.7 (8.3)	55.2 (8.5)	53.8 (8.1)	52.3 (8.0)
BMI age 18 to 21 - kg/m2, mean(SD)	20.1 (2.0)	21.5 (2.3)	22.2 (2.3)	28.8 (2.6)	22.8 (2.5)	25.3 (3.9)
BMI 1990-94 - kg/m2, mean(SD)	21.8 (1.4)	25.1 (1.5)	28.5 (1.8)	30.5 (2.4)	32.6 (2.2)	37.5 (2.7)
BMI 1995-98 - kg/m2, mean(SD)	22.4 (1.4)	25.8 (1.5)	29.3 (1.7)	31.0 (2.2)	33.6 (2.1)	38.8 (2.4)
BMI 2003-07 - kg/m2, mean(SD)	22.0 (1.7)	25.7 (1.6)	29.5 (1.8)	31.0 (2.3)	34.1 (2.2)	39.0 (2.7)
Sex, N(%)						
Male	1 443 (25.1)	5 027 (44.8)	3 936 (48.4)	535 (57.3)	995 (34.4)	218 (23.0)
Female	4 305 (74.9)	6 202 (55.2)	4 194 (51.6)	398 (42.7)	1 898 (65.6)	730 (77.0)
Country of birth, N(%)						
Australia/New Zealand	5 388 (93.7)	9 282 (82.7)	5 640 (69.4)	564 (60.5)	1 832 (63.3)	605 (63.8)
Southern Europe	360 (6.3)	1 947 (17.3)	2 490 (30.6)	369 (39.5)	1 061 (36.7)	343 (36.2)
Socio-economic indexes for areas (SEIFA) quintiles N(%)						
1 - least advantaged	724 (12.6)	1 734 (15.4)	1 554 (19.1)	205 (22.0)	672 (23.2)	235 (24.8)
2	912 (15.9)	2 143 (19.1)	1 814 (22.3)	242 (25.9)	690 (23.9)	233 (24.6)
3	843 (14.7)	1 749 (15.6)	1 354 (16.7)	141 (15.1)	480 (16.6)	181 (19.1)
4	1 177 (20.5)	2 211 (19.7)	1 515 (18.6)	151 (16.2)	525 (18.1)	143 (15.1)
5 - most advantaged	2 092 (36.4)	3 392 (30.2)	1 893 (23.3)	194 (20.8)	526 (18.2)	156 (16.5)
Level of education, N(%)						
Primary or lower	290 (5.0)	1 374 (12.2)	1 844 (22.7)	281 (30.1)	791 (27.3)	261 (27.5)
Some high/technical school	2 245 (39.1)	4 341 (38.7)	3 024 (37.2)	326 (34.9)	1 142 (39.5)	405 (42.7)
Completed high/technical school	1 335 (23.2)	2 536 (22.6)	1 654 (20.3)	173 (18.5)	549 (19.0)	163 (17.2)
Completed tertiary education	1 878 (32.7)	2 978 (26.5)	1 608 (19.8)	153 (16.4)	411 (14.2)	119 (12.6)
Mediterranean Diet Score 1990-94, N(%)						
0-3	1 753 (30.5)	3 645 (32.5)	2 763 (34.0)	358 (38.4)	1 024 (35.4)	318 (33.5)
4-6	3 238 (56.3)	6 090 (54.2)	4 373 (53.8)	481 (51.6)	1 578 (54.5)	541 (57.1)
7-9	757 (13.2)	1 494 (13.3)	994 (12.2)	94 (10.1)	291 (10.1)	89 (9.4)

Table 5 1. Characteristics of participants by BMI trajectory groups in the Melbourne Collaborative Cohort Study (continued)

	BMI Trajectory Groups					
	TR1 Lower-normal stable N=5 748	TR2 Higher-normal stable N=11 229	TR3 Normal to overweight N=8 130	TR4 Chronic borderline obesity N=933	TR5 Normal to class I obesity N=2 893	TR6 Overweight to class II obesity N=948
Mediterranean Diet Score 2003-07, N(%)						
0-3	956 (23.1)	1 732 (23.1)	1 241 (24.3)	125 (24.2)	425 (24.4)	151 (26.6)
4-6	2 515 (60.9)	4 626 (61.8)	3 181 (62.3)	328 (63.4)	1 134 (65.1)	360 (63.5)
7-9	660 (16.0)	1,128 (15.1)	681 (13.3)	64 (12.4)	182 (10.5)	56 (9.9)
Physical activity score 1990-94, N(%)						
0	866 (15.1)	2 061 (18.4)	1 985 (24.4)	243 (26.0)	859 (29.7)	318 (33.5)
>0 and <4	1 065 (18.5)	2 193 (19.5)	1 647 (20.3)	172 (18.4)	643 (22.2)	239 (25.2)
>=4 and <6	2 079 (36.2)	4 026 (35.9)	2 844 (35.0)	338 (36.2)	975 (33.7)	280 (29.5)
>=6	1 738 (30.2)	2 949 (26.3)	1 654 (20.3)	180 (19.3)	416 (14.4)	111 (11.7)
METs 2003-07, median(IQR)	21.5 (9.9, 40.0)	19.3 (8.3, 36.7)	15 (6.2, 29.8)	14 (5.0, 31.4)	11 (3.7, 24.4)	9.3 (2.8, 19.8)
Drinking status 1990-94, N(%)						
Lifetime abstainers	1 437 (25.0)	2 691 (24.0)	2 275 (28.0)	287 (30.8)	1 060 (36.6)	429 (45.3)
Ex-drinkers	195 (3.4)	376 (3.3)	315 (3.9)	58 (6.2)	121 (4.2)	43 (4.5)
Current(1-39g[male] 1-19[female])	3 460 (60.2)	6 995 (62.3)	4 734 (58.2)	516 (55.3)	1 498 (51.8)	429 (45.3)
Current(>=40 [male] >=20 [female])	656 (11.4)	1 167 (10.4)	806 (9.9)	72 (7.7)	214 (7.4)	47 (5.0)
Smoking status at last BMI measurement, N(%)						
Never	3 585 (62.4)	6 547 (58.3)	4 504 (55.4)	488 (52.3)	1 749 (60.5)	602 (63.5)
Former	1 710 (29.7)	3 905 (34.8)	3 004 (36.9)	359 (38.5)	941 (32.5)	274 (28.9)
Current	453 (7.9)	777 (6.9)	622 (7.7)	86 (9.2)	203 (7.0)	72 (7.6)
Had angina before 1990-94, N(%)	141 (2.5)	391 (3.5)	308 (3.8)	38 (4.1)	106 (3.7)	48 (5.1)
Had heart attack before 1990-94, N(%)	103 (1.8)	289 (2.6)	228 (2.8)	30 (3.2)	75 (2.6)	21 (2.2)
Had stroke before 1990-94, N(%)	37 (0.6)	124 (1.1)	94 (1.2)	13 (1.4)	25 (0.9)	12 (1.3)
Had diabetes before 1990-94, N(%)	75 (1.3)	253 (2.3)	326 (4.0)	69 (7.4)	147 (5.1)	58 (6.1)
Birth cohort, N(%)						
before 1930	1 250 (21.7)	2 725 (24.3)	1 659 (20.4)	233 (25.0)	479 (16.6)	117 (12.3)
after 1930, before 1940	1 674 (29.1)	3 662 (32.6)	2 908 (35.8)	307 (32.9)	1 028 (35.5)	310 (32.7)
after 1940, before 1950	1 999 (34.8)	3 513 (31.3)	2 639 (32.5)	298 (31.9)	1 033 (35.7)	370 (39.0)
after 1950	825 (14.4)	1 329 (11.8)	924 (11.4)	95 (10.2)	353 (12.2)	151 (15.9)

BMI, body mass index; SD, standard deviation; N, number; SEIFA, socio-economic indexes for areas; MET, metabolic equivalent; IQR, interquartile range.

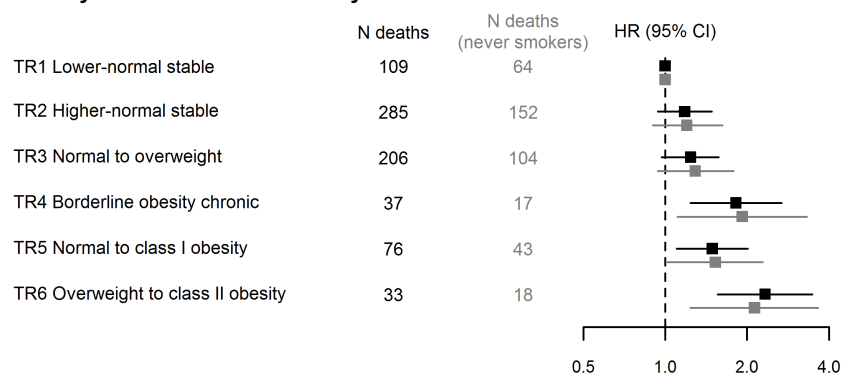
Table 5-2. Hazard ratios for all-cause mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers

BMI trajectory groups	Overall n=(29 881) ^a				Never-smokers n=(17 475) ^b			
	Person-years	Deaths	HR	(95% CI)	Person-years	Deaths	HR	(95% CI)
All-cause mortality								
TR1 Lower-normal stable	72 077	1 162	1.00		45 432	604	1.00	
TR2 Higher-normal stable	141 989	2 507	0.90	(0.84, 0.97)	83 881	1 220	0.96	(0.87, 1.07)
TR3 Normal to overweight	103 976	1 826	0.96	(0.89, 1.04)	58 515	820	1.00	(0.90, 1.12)
TR4 Borderline obesity chronic	11 711	280	1.16	(1.01, 1.33)	6 210	120	1.25	(1.02, 1.53)
TR5 Normal to class I obesity	37 235	600	1.09	(0.98, 1.21)	22 762	315	1.19	(1.03, 1.37)
TR6 Overweight to class II obesity ^c	12 357	187			7 838	107		
Age 74 years			1.31	(1.11, 1.54)			1.42	(1.13, 1.78)
Age 80 years			1.19	(1.00, 1.42)			1.27	(1.02, 1.59)
Age 85 years			1.10	(0.88, 1.38)			1.16	(0.88, 1.54)

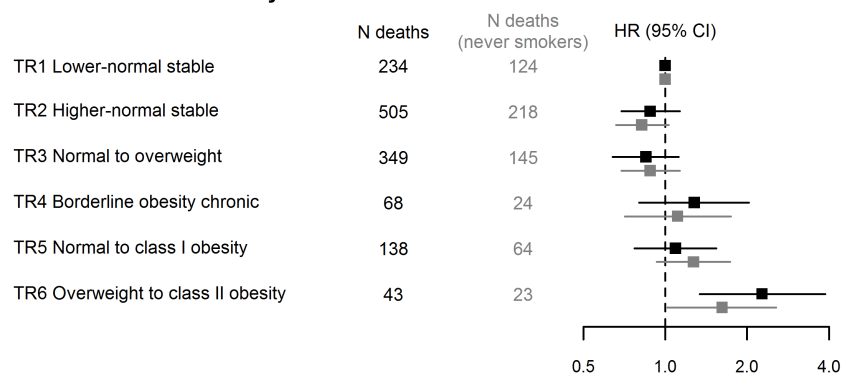
^a Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline MDS, alcohol drinking status and physical activity score. ^b Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, baseline MDS, alcohol drinking status and physical activity score. ^c p for interaction between TR6 and attained age = 0.04, tested using likelihood ratio test.

Figure 5-2. Forest plots of hazard ratios for cause-specific mortality according to BMI trajectory groups in the MCCS, overall and in never-smokers

Obesity-related cancer mortality



Cardiovascular mortality



Other-cause mortality

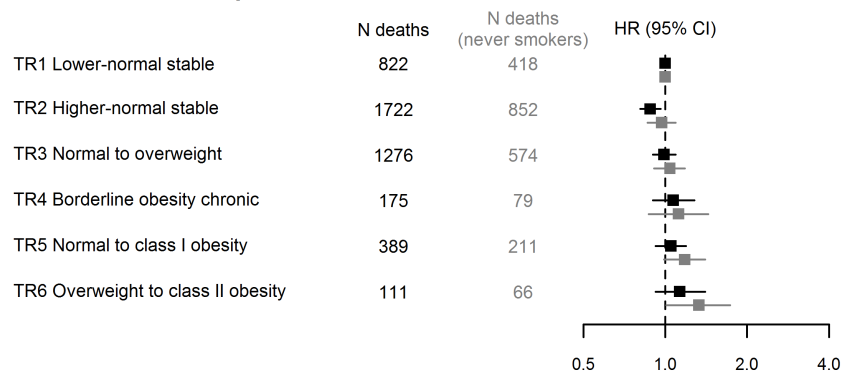


Table 5-3. Hazard ratios for all-cause mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers, excluding participants who did not attend 2003-07 data collection

BMI trajectory groups	Overall ^a n=(21 903)				Never-smokers ^b n=(13 253)			
	Person-years	Deaths	HR	(95% CI)	Person-years	Deaths	HR	(95% CI)
TR1 Lower-normal stable	52 878	655	1.00		34 655	358	1.00	
TR2 Higher-normal stable	96 021	1 283	0.88	(0.80, 0.97)	58 420	632	0.91	(0.80, 1.03)
TR3 Normal to overweight	65 825	902	0.98	(0.88, 1.09)	38 118	438	1.04	(0.90, 1.20)
TR4 Borderline obesity chronic	6 624	124	1.21	(0.99, 1.47)	3 643	65	1.36	(1.04, 1.79)
TR5 Normal to class I obesity	22 598	280	1.13	(0.98, 1.30)	14 114	164	1.22	(1.01, 1.48)
TR6 Overweight to class II obesity ^c	7 125	83			4 768	50		
Age 74 years			1.43	(1.13, 1.83)			1.61	(1.17, 2.20)
Age 80 years			1.08	(0.84, 1.39)			1.19	(0.86, 1.65)
Age 85 years			0.85	(0.62, 1.17)			0.93	(0.62, 1.39)

^a Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline MDS, alcohol drinking status and physical activity score. ^b Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, baseline MDS, alcohol drinking status and physical activity score. ^c p for interaction between TR6 and attained age = 0.0002 for overall and 0.003 for never-smokers, tested using likelihood ratio test.

DISCUSSION

Most participants had normal BMI at age 18-21 years. We identified six BMI trajectories. Most participants maintained a higher-normal BMI throughout adulthood or gained weight from higher-normal to become overweight. Only a small proportion of people developed class II obesity in mid to late life. Generally, the lowest mortality was experienced by participants who maintained higher-normal BMI throughout adulthood. Participants who were obese across the midlife had elevated all-cause mortality, even if they had normal BMI at younger age as did those who had prolonged exposure to borderline obesity. These associations were stronger for never-smokers and for obesity-related cancer deaths. Being overweight in early adulthood and becoming class II obese was associated with higher CVD mortality.

The key strength of our study is availability of weight at multiple times, which was used to derive trajectories in BMI across adulthood. This approach allowed us to categorise BMI over time into homogeneous groups and to identify a specific higher-risk group (i.e., prolonged borderline obesity trajectory) that would not have been identifiable using the conventional approach of grouping participants into categories of change.

Several limitations should be noted. For some trajectories, there were few cause-specific deaths, with corresponding wide confidence intervals. Recalled weight at age 18-21 years may be subject to measurement error. However, previous studies have generally found moderate to strong correlation between measured weight in young adulthood and recalled weight for the same age 32 to 56 years later.^{224,225} We did not have information on potential confounders at age 18-21. We also had no information on weight between age 18-21 years and baseline (20-50 years later), which limited us from identifying trajectories of how people gained weight after age 18-21 years and before entering the study in midlife. Participants excluded due to insufficient BMI records had higher BMI at age 18-21 and baseline. Having insufficient BMI records was also associated with higher odds of dying. Therefore, we may have underestimated the effect of obese trajectories on all-cause mortality.

Participants were mostly born before 1950. Few people (2%) had BMI of 30 or higher at age 18-21 years. Hence, we were not able to estimate the effect of sustained obesity from young adulthood. The prevalence of overweight in Australia has increased in cohorts born since 1960; the mean BMI has been higher for each successive birth cohort at any given age.²²⁶ The prevalence of childhood overweight and obesity has also increased globally.²²⁷⁻²²⁹ In Australia, the proportion of obese individuals at age 18-21 years was almost double in people born in 1994-1997 (15.2%) compared with their counterparts born 20 years earlier (8%).²³⁰ The projected

increase of obesity prevalence in young adults ²³¹ also suggests that potential higher-risk trajectories of chronic and severe obesity may emerge. Therefore, it is expected that more people in future generations will have higher BMI for longer durations. Conventional analytic approaches using a single BMI assessment or an *a priori* categorization of body size changes could overlook these potential high-risk groups. Trajectories models may help differentiate people who have been obese long-term from those who become obese later in life.

Some studies have reported lower all-cause mortality in overweight individuals than for normal weight individuals.^{10,11} However, we did not observe lower risk of death in participants who were overweight in midlife (TR3). The US Health and Retirement Study (HRS) modelled BMI trajectories from 51 to 77 years for adults aged 51 to 61 years at baseline, and found that people with sustained overweight had the lowest all-cause mortality.⁵³ The National Survey of the Japanese Elderly identified no obesity in trajectories in a Japanese population aged 60 years and older, with only 5% ‘overweight stable’ individuals.⁵⁴ The lowest risk of death was observed for participants with sustained overweight overall, but not in non-current smokers.⁵⁴ However, these two studies only used BMI data in mid to late life. A study of health professionals in the US using earlier life (age 5 to 50 years) body shape pictograms found that people remaining lean had the lowest mortality; people who experienced a marked increase from lean to heavy had a higher risk; whereas people who had been heavy since childhood were at highest risk.⁵⁵ However, many participants in the study were not obese according to their BMI, even when they were classified as ‘heavy’ based on pictogram. Possible measurement errors in body shape data (i.e., combining recalled somatotypes with BMI-predicted somatotypes) may have affected their trajectory shapes. Nevertheless, their results showed that larger body shapes from childhood are likely to persist into adulthood, that being consistently heavy is associated with increased risk of death from all-cause, CVD, and cancer, and the increased risk was stronger for never-smokers.⁵⁵ Another study of 70,000 men showed that both ‘normal to obese’ and ‘overweight to obese’ adulthood BMI trajectories were associated with higher mortality from fatal prostate cancer compared with stable normal BMI trajectory.⁵⁷

In our study, participants who had long-term borderline obesity also had increased risk of death compared with lower-normal BMI trajectory. Long-term obesity gives longer exposure to pro-inflammatory adipocytokines released by adipose tissue, which can lead to pathophysiological alterations such as dyslipidaemia, hypertension, fibrinolysis, inflammation, insulin resistance and immune system alterations.³⁶⁻³⁸ Obesity also increases bioavailable estrogens (via aromatization, the conversion of adrenal androgens to estrone, in adipose tissue),^{232,233} a contributing factor to breast and gynecological cancers. Long-term obesity may also be

associated with partial exhaustion of the beta cell and insulinopenia which might cause depressed glucose oxidation and impaired glucose tolerance.²³⁴ Longer duration of obesity is associated with several adverse health consequences that could contribute to increased mortality, including unfavourable biomarker profiles as indicated by higher C-peptide and lower IGFBP-1 concentrations,³⁹ type 2 diabetes,^{40,41} cancer,^{42-44,57} and cardiovascular disease.⁴⁵

A systematic review of studies using baseline BMI showed that all-cause mortality was higher for older people who had a BMI <23.0 kg/m².²³⁵ In older populations such as the National Survey of the Japanese Elderly, most people followed trajectories with a gradual decline in BMI over time.⁵⁴ Relative to the 'mid-normal decreasing' group, all-cause mortality was higher in the 'low-normal decreasing' group (HR=1.17, CI: 1.02 to 1.33) and lower in the 'high-normal decreasing' group (HR=0.82, CI: 0.72 to 0.93). This suggests that for older people experiencing weight loss, a higher initial BMI may be protective. In our study, the estimated effect of being overweight in early adulthood and gaining weight in midlife (TR6) declined with age. This is consistent with the results of a study investigating weight change with different initial BMI levels in relation to all-cause mortality in older Americans.²¹² The authors found that compared with having a stable weight, even a small weight loss in the elderly was associated with increased mortality in normal weight, overweight and even mildly obese individuals.²¹² This association was stronger when initial BMI was lower.²¹² Similarly, in a previous analysis of weight change and mortality using the MCCS, weight loss from 1990-94 to 2003-07 (i.e., in later adulthood) was associated with higher risk of death.²¹³ Weight loss in older people can be an indicator of undesirable health conditions such as sarcopenia,²³⁶ or a more severe disease state.²³⁷ Individuals with higher body weight may tolerate weight loss better than individuals with a normal body weight because of higher metabolic reserves and body fat.²³⁷ Measures of body composition and fat distribution are needed to capture more adequately the relationship of adiposity and lean mass to health risks in older populations.²³⁸

CONCLUSION

Midlife obesity was associated with higher mortality even when BMI was normal in early adulthood. This highlights the importance of weight management throughout adulthood. Prolonged borderline obesity was also associated with elevated risk of death from all-causes and obesity-related cancers relative to maintaining lower-normal BMI across adulthood. Since chronic obesity will likely be a major health issue for future generations, policies and prevention programs are needed to target obesity starting early in life.

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AUTHORS' CONTRIBUTIONS

YY, PAD, BML, AMH and DRE conceived and planned the project; YY performed the statistical analyses and drafted the manuscript with support from PAD, BML, AMH and DRE; AK, RJM, RLM and GGG provided critical feedback and helped shape the research, analysis and the final manuscript. GGG conceived the overall study. All authors approved the final manuscript.

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COMPETING INTERESTS

None declared.

PARTICIPANT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

The research protocol was approved by Cancer Council Victoria's Human Research Ethics Committee.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

Chapter 6 Sustained hypothetical interventions on physical activity and TV viewing in relation to all-cause mortality

Objective 3 of the thesis is to estimate the effects of sustained physical activity and sedentary behaviour over adulthood on mortality. To address Objective 3, I analysed data from the AusDiab study. This chapter presents the authors accepted version of the following paper published in *Medicine and Science in Sports and Exercise*:

Yi Yang, Allison M. Hodge, Pierre-Antoine Dugué, Elizabeth J. Williamson, Paul A. Gardiner, Elizabeth L.M. Barr, Neville Owen, David W. Dunstan, Brigid M Lynch, Dallas R English. Mortality effects of hypothetical interventions on physical activity and TV viewing. *Medicine & Science in Sports & Exercise* 2021;53(2):316-323. DOI: 10.1249/mss.0000000000002479.

Supplementary material related to this publication is included in Appendix C.

Mortality effects of hypothetical interventions on physical activity and TV viewing

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ABSTRACT

Introduction Long-term effects of physical activity and TV viewing on mortality have been inferred from observational studies. The associations observed do not allow inferences about the effects of population interventions and could be subject to bias due to time-varying confounding.

Methods Using data from the Australian Diabetes, Obesity and Lifestyle Study, collected in 1999-2000 (T0), 2004-05 (T1), and 2011-12 (T2), we applied the parametric g-formula to estimate cumulative risks of death under hypothetical interventions on physical activity and/or TV viewing determined from self-report, while adjusting for time-varying confounding.

Results In the 6,377 participants followed for 13 years from 2004-05 to death or censoring in 2017, 781 participants died. The observed cumulative risk of death was 12.2%. The most effective hypothetical intervention was to increase weekly physical activity to >300 minutes (RR=0.66, 0.46 to 0.86 compared with a 'worst-case' scenario; and RR=0.83, 0.73 to 0.94 compared with no intervention). Reducing daily TV viewing to <2 hours in addition to physical activity interventions did not show added survival benefits. Reducing TV viewing alone was least effective in reducing mortality (RR=0.85, 0.60 to 1.10 compared with the worst-case scenario; and RR=1.06, 0.93 to 1.20 compared with no intervention).

Conclusion Our findings suggested that sustained interventions to increase physical activity could lower all-cause mortality over a 13-year period and there might be limited gain from intervening to reduce TV viewing time in a relatively healthy population.

Keywords: time-varying confounding, hypothetical interventions, g-formula, cohort study

INTRODUCTION

Both insufficient physical activity (i.e., not meeting physical activity recommendations) and sedentary behaviour (time spent sitting, as distinct from lack of physical activity) contribute to risk of chronic disease and mortality. In the absence of evidence from randomized trials to quantify the long-term effects of changes in physical activity and sedentary behaviour, understanding how they are jointly related to mortality could be enhanced by better exploiting data from observational studies.¹⁰⁶

Insufficient physical activity and time spent in sedentary behaviours, particularly television (TV) viewing, have been associated with higher all-cause mortality in observational studies.^{100,239} These studies have typically measured exposures and confounders at a single time point, so did not assess the possible impact of exposure changes over follow-up. We have previously highlighted²⁴⁰ that in studies that used data from multiple time points, conventional regression analyses can be problematic in the presence of time-varying confounding when the values of confounding variables are influenced by past exposures (e.g. sedentary behaviour affects adiposity, which in turn affects physical activity at the next time point).^{206,207} When there is time-varying confounding, conditioning on confounders (e.g. adiposity) that also lie in a causal pathway in standard regression models can produce biased estimates (see Supplementary Figure 6-1, which illustrates an example of time-varying confounding affected by prior exposure).¹⁸⁵ Alternative methods such as inverse probability weighting of marginal structural models have been used to estimate causal effects of physical activity while adjusting for such time-varying confounding.^{122,165,241-243} No published studies on sedentary behaviour with multiple observation points have accounted for time-varying confounding.

Insufficient physical activity and sedentary behaviour can be viewed as separate risk factors with distinct sociodemographic and behavioural contexts and correlates.¹⁰⁵ Our aim was to estimate the effects of single or joint hypothetical interventions for insufficient physical activity and a common leisure-time sedentary behaviour, TV viewing, on all-cause mortality over an approximate 13-year period, while accounting for time-varying confounding, using the parametric g-formula. We used the parametric g-formula because it allows estimation of the causal effects of complex population interventions, which could inform policy more directly compared with a typical exposure effect.²⁴⁴

METHODS

Study population

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) is a population-based cohort study conducted in the six states and the Northern Territory of Australia. Details about the cohort have been described.¹⁹¹ Briefly, participants aged at least 25 years were recruited in 1999-2000 (T0), then followed up in 2004-05 (T1), and 2011-12 (T2). Each data collection involved an initial household interview, followed by a biomedical examination and the administration of questionnaires. In the present study, we used T1 (2004-05) as baseline in order to have information on pre-baseline exposure and confounder history. Participants who attended T1 data collection (n=6,400) were included in this analysis. Participants who were pregnant (n=23) at data collections were excluded, which left 6,377 participants eligible for the analysis. The study was approved by the Ethics Committee of the International Diabetes Institute and all participants provided informed consent.

Exposure measurements

Self-reported frequency and duration of leisure-time physical activity (LTPA) during the previous week was measured using the Active Australia Survey.¹⁹⁶ The questions have been shown to have good reliability and validity.¹⁹⁶ Physical activity consisted of walking for recreation or transport, moderate-intensity and vigorous-intensity physical activity at leisure-time. Total weekly recreational physical activity time was calculated as the sum of the time spent walking continuously for at least 10 minutes, time performing moderate physical activity, and double the time spent in vigorous physical activity ($Time_{LTPA} = Time_{walk} + Time_{moderate} + 2 \times Time_{vigorous}$).¹⁹⁶ The total time of weekly physical activity during leisure-time was later used to simulate hypothetical interventions.

Participants were asked to self-report time spent watching TV or videos in the last 7 days, but to exclude the time that this occurred while performing other activities such as preparing a meal or doing other household chores. This method has been shown to provide reliable and valid estimates of TV viewing time among adults.²⁴⁵ Average daily TV viewing hours was calculated.

Confounder measurements

Information on demographic attributes (sex, baseline age, country of birth, and level of education), self-reported history of health conditions (high cholesterol, high blood pressure,

heart disease, and diabetes), and smoking status was obtained by an interviewer-administered questionnaire.¹⁹¹ Total cholesterol, hypertension and diabetes status were also measured in the biomedical examinations. However, we used the self-reported history of diagnosis, assuming that awareness of prior health conditions would have more influence on an individual's lifestyle behaviours. Quintiles of an area-based index of relative socioeconomic advantage and disadvantage was calculated based on participants postcode of residence.²⁴⁶ Alcohol and dietary intake were assessed using a self-administered, validated food frequency questionnaire. Mediterranean diet score was computed and used as a measure of overall diet quality.¹⁹⁵ General health was assessed using the self-administered SF-36 questionnaire. Waist circumference was measured by trained staff.¹⁹¹ We used waist circumference instead of BMI because there is evidence it is a stronger predictor of all-cause mortality than BMI.²⁴⁷

Death ascertainment

Vital status and date of death were determined by linkage to the Australian National Death Index. Participants were followed until the date of death or administrative end of follow-up on 17 April 2017.

Hypothetical interventions

We considered the following hypothetical interventions at T1 and T2, based on guidelines for physical activity²⁴⁸ and the associations between TV viewing time and metabolic biomarkers²⁴⁹: increasing weekly physical activity to sufficient (i.e., 150 to 300 minutes) if insufficiently active (i.e., <150 minute); increasing weekly physical activity to optimal (i.e., >300 minutes) for all participants; reducing daily TV viewing to <2 hours for all participants; increasing weekly physical activity to sufficient if insufficiently active and reducing daily TV viewing to <2 hours; and, increasing weekly physical activity to >300 minutes and reducing daily TV viewing to <2 hours for all participants.

In addition, for comparison, we considered a no-intervention scenario in which physical activity level and TV viewing time were allowed to evolve naturally (typically referred to as the 'natural course'), and a scenario where weekly physical activity decreased to less than 30 minutes and daily TV viewing increased to 4 hours or more for all participants (i.e., worst-case scenario).

Statistical analysis

We used the parametric g-formula to estimate the 13-year cumulative risk of death under various hypothetical interventions on physical activity and/or TV viewing. The parametric g-

formula is a generalization of standardization for time-varying exposures and confounders and can be used to estimate the standardized risk of death for hypothetical interventions under the assumptions of no unmeasured confounding, no measurement error and no model misspecification.²⁰⁷ The standardized risk is estimated by a weighted average of the risks of death conditional on the given intervention and the observed confounder history. The weights are probability distribution functions of the time-varying confounders estimated using parametric regression models. The weighted average is approximated through Monte Carlo simulation.²⁵⁰ We implemented the parametric g-formula in two steps. First, parametric models were fitted to model conditional probabilities of physical activity, TV viewing, and each of the following time-varying confounders in the order listed: self-reported history of high cholesterol (yes; no), high blood pressure (yes; no), heart disease (yes; no), and diabetes (yes; no), self-reported general health status (excellent; very good; good; fair; poor), waist circumference (normal: <94cm [male] or <80cm [female]; increased risk: 94cm to <102cm [male] or 80cm to <88 cm [female]; greatly increased risk: ≥102cm [male] or ≥88 [women]²⁵¹), Mediterranean diet score (0–3; 4–6; 7–9¹⁹⁵), smoking status (never; former; current), and alcohol intake (gram/day: 0 [Male & Female]; 1–39 [Male]/1–19[Female]; 40–59[Male]/20–39[Female]; 60+[Male]/40+[Female]²⁵²). The models also included the following time-fixed confounders: sex (male; female), baseline age (years), quintiles of an area-based index of relative socioeconomic advantage and disadvantage,²⁴⁶ country of birth (Australia or New Zealand; others), and level of education (university or technical institution; completed high school; some high school; primary/never attended school). See Supplementary Table 6-1, for details of models. These models were then used to simulate risk of death while setting physical activity and TV viewing to a specified intervention level in a Monte Carlo sample of the same size: 1) T0 and T1 confounder values were retained for all participants; T1 physical activity and TV viewing values were set to a specific level if part of an intervention; 2) risk of death before T2 was simulated; 3) for participants simulated to remain alive at T2: physical activity and TV viewing were set to a specific level if part of an intervention, T2 values of confounders were simulated by comparing the predicted probability of the confounder value to a value randomly drawn from a standard uniform distribution, and risk of death from T2 to the end of follow-up was simulated; 4) cumulative risk of death (i.e., 13-year risk) was calculated as:

$$P_{13\text{-year}} = P_{\text{death before T2}} + (1 - P_{\text{death before T2}}) P_{\text{death after T2}}.$$

For each hypothetical intervention, we compared the estimated 13-year risk of death with the risk under the natural course (i.e., no-intervention scenario) and the risk under the worst-case

scenario by calculating the risk ratios (RR) and risk differences (RD). We conducted the analyses separately in female and male participants to examine the possibility of effect heterogeneity by sex. We also compared simulated risk of death under the natural course with the observed risk as an informal validation of correct gross model specification.

Multiple imputation by chained equations (MICE) was used to impute missing data (due to missing response to the questionnaire, or missing T2 attendance for those who were still alive at T2) under the assumption that data were missing at random, i.e., the probability of data being missing did not depend on the unobserved data, conditioning on the observed data.²⁵³ For each hypothetical intervention, point estimates were averaged over 40 imputed datasets; For the main analysis, 500 bootstrap samples were drawn for each imputed data set to estimate the standard errors and 95% confidence intervals were calculated using Rubin's rule ^{254,255}; for sensitivity analyses, 200 bootstrap samples were used.

For comparison with a conventional approach, Cox regression with age as the time scale was used to estimate hazard ratios for mortality associated with baseline TV viewing and physical activity, adjusting for baseline confounders.

Statistical analyses were performed using Stata version 14.2 (StataCorp, Texas, USA), and Stata version 15 on the University of Melbourne's high performance computing platform (Spartan).

RESULTS

A total of 6,377 participants (54.7% female) were eligible. During 13 years (73,518 person years) of follow-up, 781 participants died (373 pre-T2 and 408 post-T2). Of participants who were alive at T2 (n=6,004), 20% did not attend T2 data collection. Participants who attended T2 were overall younger, from more socio-economically advantaged areas, and had higher educational qualifications than participants who were alive but did not attend T2; a higher proportion of them reported good to excellent health in general, and no history of health conditions at T1 (see Supplementary Table 6-2, characteristics of participants who were alive but did not attend T2).

Table 6-1 shows the characteristics of eligible participants at baseline (T1), and the potential time-varying confounders pre- and post-baseline. Mean age at baseline was 56.5 years. Three quarters (75.9%) were born in Australia or New Zealand and 40.2% had tertiary education. At baseline, more than half of the sample were sufficiently active (57%) or watched less than 2

hours of TV (54%) (Table 6-1). Active participants tended to spend less time watching TV daily, although the differences were not large (Figure 6-1).

Table 6-1. Characteristics of participants included in the analysis (AusDiab study)

	1999-2000 (T0)	2004-05 (T1)	2011-12 (T2)
Time-fixed covariates			
Baseline age (years), mean(SD)		56.5 (12.8)	
Sex, N(%)			
Male		2891 (45.3)	
Female		3486 (54.7)	
Born in Australia/New Zealand, N(%)		4839 (75.9)	
The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), N(%)			
1 (greatest disadvantage)		1084 (17.3)	
2		1296 (20.7)	
3		1291 (20.6)	
4		1204 (19.2)	
5 (greatest advantage)		1395 (22.2)	
Level of education, N(%)			
University or technical institution		2561 (40.2)	
Completed high school		1460 (22.9)	
Some high school		1966 (30.8)	
Primary or never attended school		390 (6.1)	
Baseline height(cm), mean(SD)		167.6 (9.6)	
Time-varying covariates			
Weekly Physical activity, N(%)			
< 30 minutes	1257 (19.9)	1099 (17.4)	729 (15.8)
30 to 149 minutes	1686 (26.7)	1626 (25.7)	1127 (24.4)
150 to 300 minutes	1368 (21.6)	1480 (23.4)	1074 (23.3)
> 300 minutes	2015 (31.9)	2118 (33.5)	1680 (36.4)
Daily TV viewing time, N(%)			
< 2 hours	3655 (57.7)	3385 (53.6)	2030 (52.7)
2 to 4 hours	2225 (35.1)	2340 (37.0)	1478 (38.3)
≥ 4 hours	459 (7.2)	595 (9.4)	347 (9.0)
Mediterranean Diet Score, N(%)			
0-3	1870 (29.3)	1922 (30.7)	1067 (29.7)
4-6	3766 (59.1)	3695 (59.0)	2127 (59.3)
7-9	741 (11.6)	651 (10.4)	394 (11.0)
Waist circumference ^b , N(%)			
Normal	2500 (39.6)	2120 (33.3)	1057 (26.8)
Increased risk	1641 (26.0)	1654 (26.0)	1007 (25.5)
Greatly increased risk	2173 (34.4)	2584 (40.6)	1879 (47.7)

N: number; SD: standard deviation. Numbers across categories for some variables did not add up because of missing values.^aNumber of participants attended T2, before multiple imputation was applied to impute missing data due to missing T2 attendance for those who were still alive at T2. ^bNormal, <94 cm (male) or <80 cm (female); increased risk, 94 to <102 cm (male) or 80 to <88 cm (female); greatly increased risk, ≥102 cm (male) or ≥88 (women).

Figure 6-1. Plot of daily TV viewing and weekly physical activity at baseline (T1)

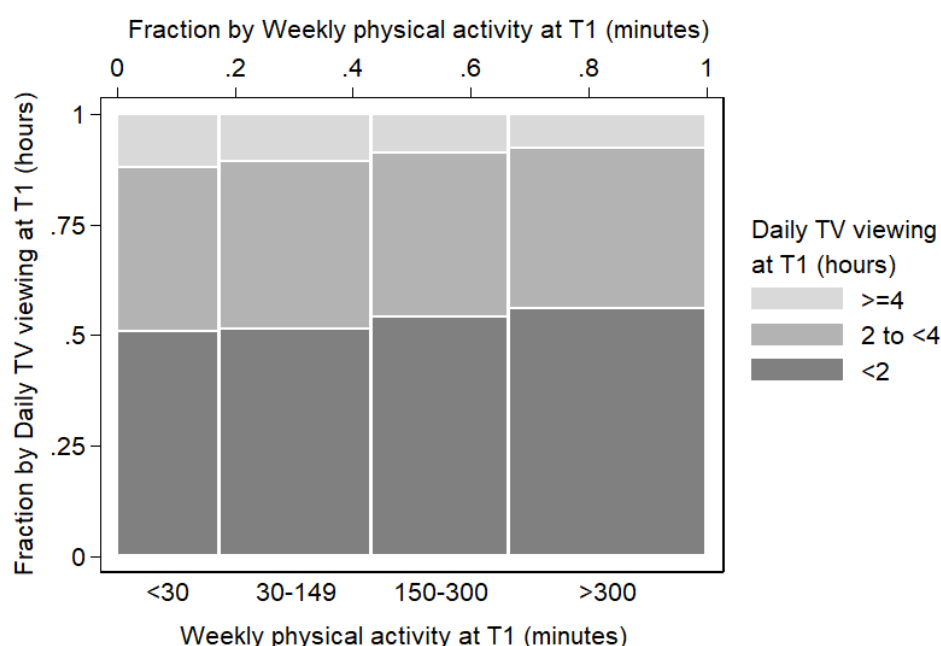


Table 6-2 shows the 13-year risks of death under various hypothetical interventions. The simulated 13-year risk of death under no intervention (12.1%) was very similar to the observed risk (12.2%), indicating that the models were correctly specified overall. The hypothetical intervention that reduced 13-year risk of death the most was to improve physical activity to >300 mins/week (RR=0.83, 0.73 to 0.94 compared with the natural course; and RR=0.66, 0.46 to 0.86 compared with the worst-case scenario), followed by improving physical activity to 150-300 mins/week for insufficiently active participants (RR=0.92, 0.82 to 1.01 compared with the natural course; and RR=0.73, 0.52 to 0.94 compared with the worst-case scenario). The average percentages of participants who needed to improve their physical activity were 65.2% and 42.1%, respectively for the two interventions. The intensive physical activity intervention would have prevented 20 deaths (CI: 7 to 33 deaths) per 1000 people in a 13-year period compared with not intervening. Reducing daily TV viewing to < 2 hours alone was the least effective intervention for lowering mortality (RR=1.06, 0.93 to 1.20 compared with the natural course; and RR=0.85, 0.60 to 1.10 compared with the worst-case scenario). Reducing daily TV hours jointly with any of the physical activity interventions required more people changing their behaviours (average of 80.7% and 68.2%, respectively), while not lowering the risk further.

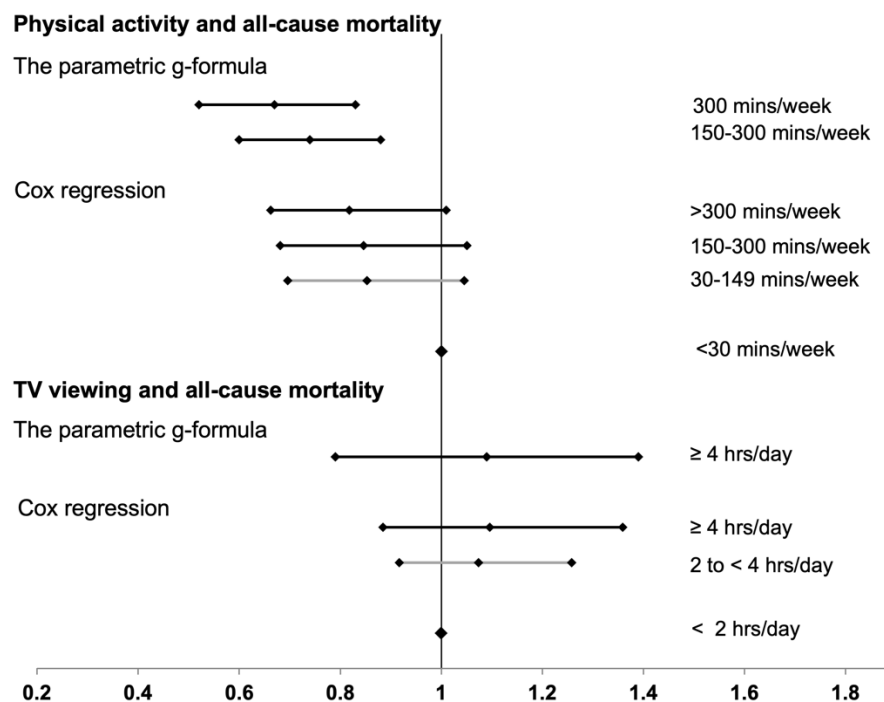
Table 6-3 shows the 13-year risk of death in male and female participants under the natural course, the worst-case scenario, and the joint intensive intervention. The effect of hypothetical

interventions on mortality (i.e., risk ratios) appeared to be similar for male and female participants. However, population risk difference was larger in males than in females because of higher absolute risks under the natural course.

We assumed correct ordering of exposures and time-varying confounders in our models. Our sensitivity analysis showed that results were robust to various modelling orders (see Supplementary Table 6-3, estimated risk of death under various modelling orders of time-varying covariates).

We found that the usual method of analysis, which used only baseline data in a Cox regression model underestimated the benefit of sustained higher physical activity compared with the g-formula, but the effect of TV viewing on all-cause mortality estimated from the g-formula was similar to the effect estimated from the Cox regression (Figure 6-2).

Figure 6-2. Effects of TV viewing and physical activity on all-cause mortality, estimated by g-formula and Cox regression



The parametric g-formula (risk ratio and 95% CI) adjusted for time-fixed and time-varying confounding. Risk ratios for the '2 to <4 hours' TV viewing category and the '30-149 mins/week' physical activity category were not presented because we did not simulate these hypothetical interventions. Cox model (hazard ratio and 95% CI) adjusted for baseline (T1) confounders (i.e., typical adjustment of baseline confounders). Five imputations were used because of 5% T1 missing data. For comparison, '< 2 hours' TV viewing and '<30 mins/week' physical activity were used as reference categories in both the parametric g-formula analysis and the Cox model.

Table 6-2. Risks of death under hypothetical interventions using the parametric g-formula

No.	Interventions		13-year risk of death (%), 95% CI	Population risk difference (%), 95% CI	Population risk ratio, 95% CI	Risk difference (%), 95% CI	Risk ratio, 95% CI	Average % needed intervention ^a
0	Natural course	No intervention	12.1 (10.9 to 13.2)	Reference	Reference			0
1	Worst-case scenario	Reducing physical activity to <30 mins/week, and increasing TV viewing to ≥4 hrs/day for all	15.2 (11.6 to 18.9)	3.2 (-0.4 to 6.8)	1.26 (0.96 to 1.57)	Reference	Reference	97.6
2	Physical activity only, moderate	Increasing physical activity to 150-300 mins/week if <150 mins/week	11.1 (9.7 to 12.4)	-1.0 (-2.2 to 0.2)	0.92 (0.82 to 1.01)	-4.2 (-8.2 to -0.2)	0.73 (0.52 to 0.94)	42.1
3	Physical activity only, intensive	Increasing physical activity to >300 mins/week for all	10.0 (8.6 to 11.5)	-2.0 (-3.3 to -0.7)	0.83 (0.73 to 0.94)	-5.2 (-9.3 to -1.1)	0.66 (0.46 to 0.86)	65.2
4	TV viewing only	Reducing TV viewing to <2 hrs/day if ≥2 hrs/day	12.8 (11.1 to 14.6)	0.8 (-0.9 to 2.4)	1.06 (0.93 to 1.20)	-2.4 (-6.6 to 1.8)	0.85 (0.60 to 1.10)	48.4
5	Joint, moderate	Intervention No. 2 and No.4	11.6 (9.8 to 13.3)	-0.5 (-2.1 to 1.1)	0.96 (0.83 to 1.09)	-3.7 (-8.0 to 0.7)	0.76 (0.52 to 1.01)	68.2
6	Joint, intensive	Intervention No. 3 and No.4	10.5 (8.7 to 12.4)	-1.5 (-3.3 to 0.2)	0.87 (0.73 to 1.02)	-4.7 (-9.2 to -0.2)	0.70 (0.46 to 0.93)	80.7

The observed 13-year risk of death was 12.2%; 500 bootstrap samples were drawn for each of the 40 imputed datasets to estimate the standard errors and 95% CIs. ^a Average percentage of participants who need to be intervened on at T1 and T2.

Table 6-3. Risks of death under hypothetical interventions in women and men.

Interventions	13-year risk of death (%), 95% CI	Population risk ratio, 95% CI	Population risk difference (%), 95% CI	Risk ratio, 95% CI	Risk difference (%), 95% CI
Women					
Natural course	9.9 (8.4 to 11.3)	Reference	Reference		
Worst-case scenario	12.5 (8.0 to 16.9)	1.27 (0.83 to 1.70)	2.6 (-1.6 to 6.8)	Reference	Reference
Joint, intensive	8.7 (6.1 to 11.3)	0.88 (0.61 to 1.15)	-1.2 (-3.8 to 1.4)	0.70 (0.31 to 1.09)	-3.8 (-9.6 to 2.0)
Men					
Natural course	14.7 (13.1 to 16.4)	Reference	Reference		
Worst-case scenario	19.1 (12.9 to 25.2)	1.30 (0.88 to 1.71)	4.3 (-1.8 to 10.5)	Reference	Reference
Joint, intensive	12.7 (9.7 to 15.7)	0.86 (0.68 to 1.04)	-2.0 (-4.7 to 0.7)	0.67 (0.36 to 0.98)	-6.4 (-14.0 to 1.3)

The observed 13-year risk of death was 9.8% for women, and 15.2% for men; 200 bootstrap samples were drawn for each of the 40 imputed datasets to estimate the standard errors and 95% CIs.

DISCUSSION

Our results suggest that in this cohort of adults, mortality could have been lowered by sustained interventions that increased physical activity. The intervention that appeared most effective to reduce mortality compared with no intervention was to increase weekly physical activity to >300 minutes (the intensive physical activity intervention), followed by increasing physical activity to 150-300 minutes/week in people who were insufficiently active (the moderate physical activity intervention). Interventions that reduced TV viewing time alone or in addition to physical activity interventions did not show added mortality benefits.

Although the intensive physical activity intervention was the most effective in reducing mortality, it required more participants to modify their behaviour to achieve the change (on average, 65% of participants needed to modify their physical activity levels at each time point), compared with the moderate physical activity intervention (42% on average needs to change). A systematic review found that relative reduction in all-cause mortality associated with higher physical activity was greater for females than for males,¹⁰² the effects of the hypothetical interventions on relative reduction in mortality were similar for females and males in our study. It should be noted that in real life incomplete adherence is likely, and our estimates correspond to the best-case scenario.

Like other analyses of observational data, these estimates are based on the assumptions of no unmeasured confounding, no measurement error, and no model misspecification. We cannot exclude the possibility of unmeasured confounding despite adjusting for several important confounders. Self-reported time spent in physical activity and TV viewing are subject to measurement error. However, the questionnaires used in our study were previously shown to have good reliability and acceptable validity for estimates of the true exposure level.^{196,245} We acknowledge the possibility of misspecification of parametric models and functional forms of the past covariate history included as independent variables. However, we were able to closely reproduce the observed risk of death under the natural course, which is a necessary condition for no overall model misspecification under no intervention. The parametric g-formula requires fitting multiple models, therefore it may be more sensitive to violations of the above assumptions, as violation in one model may accumulate through the others.²⁵⁰ The parametric g-formula is subject to the ‘g-null paradox’, i.e., the null hypothesis, (in our case, this is that interventions on physical activity and TV viewing have no effect on all-cause mortality), even if true, will be rejected in a large enough sample because the estimated value of the g-formula for the outcome generally depends on the exposure history²⁵⁶. However, in practice, the g-null

paradox is of less concern compared with typical random variability.²⁰² Finally, the imputation of missing data relied on the missing-at-random assumption, which was reasonably plausible given the extensive risk factor information collected at each time point.

Current public health guidelines recommend minimizing sedentary behaviour and doing at least 150 mins/week of moderate-to-vigorous-intensity physical activity, or 300 mins/week for additional health benefit.¹⁰⁹⁻¹¹¹ These recommendations are mainly based on studies of associations between exposures at a single time point and risk of health outcomes such as cardiovascular health and cancer.¹¹⁰ Our study, on the other hand, estimated the potential impact on mortality had these two risk factors been altered by sustained population interventions. This is the key strength of our study, because it is rarely feasible to estimate such causal effects for a generally healthy population through randomized controlled trials.¹⁰⁶ Our finding demonstrated that using a single measurement of physical activity is likely to underestimate the protective effects of physical activity. This may stimulate additional public health expenditure into physical activity promotion. Health promotion programmes frequently incorporate physical activity promotion into programmes to address obesity prevention or reduction. Our research (which accounts for obesity-related time-varying confounding) highlights that physical activity itself is important for longevity. Although other g-methods such as inverse probability weighted marginal structural models could also overcome the bias from time-varying confounding affected by past exposure through generating a pseudo-population in which exposure is independent of confounders, the parametric g-formula has the advantage of generating counterfactual outcomes under different exposure scenarios that involve multiple interventions such as increasing physical activity *and* reducing TV time.¹⁸⁵

Previous findings from the AusDiab study reported that watching ≥ 4 hours of TV daily was associated with higher all-cause mortality.²⁵⁷ Our Cox model showed a weaker association in the same direction between TV viewing time at T1 and all-cause mortality (Figure 6-2). This could be partly because the previous study used T0 as baseline, whereas we used T1 as baseline. Our sample was smaller due to loss to follow-up between T0 and T1, and healthier. The prevalence of self-reported excellent and very good health status was slightly lower in participants than in the general Australian population.²⁵⁸ However, the participants were more physically active than the general Australian population of the same age – about 50% at T0 reported sufficient levels of activity (see Supplementary Table 6-4, pre-baseline characteristics of participants by baseline attendance status) compared with about 40% for the population.²⁵⁹ Thus, our findings might be most applicable to physically active people. In our sample where

daily TV viewing hours were already below two hours for more than half of the participants, we estimated no further survival benefit by intervening on this exposure. Over the 12 years between T0 (1999/2000) and T2 (2011/2012), there was an expansion of television viewing options, and other domestic entertainment and screen-based technologies, which may have reduced the relevance of our exposure variable. Although our estimates are not directly comparable to results from studies using conventional regression approaches, our findings and those of studies using regression approaches suggest protective effects of physical activity on mortality.¹⁰² Furthermore, we found that using only baseline data could underestimate the potential benefit of long-term physical activity.

Although we used repeatedly measured exposure data, the analyses would have benefited from more time points at regular intervals, which are more representative of sustained interventions over time. We coarsened the time spent in physical activity and TV viewing into categories relevant to current public health guidelines. This may affect the interpretation of our findings because of multiple versions of treatment.²⁶⁰ For example, our hypothetical intervention, “increasing physical activity to > 300 mins/week” can be achieved by increasing physical activity to 301 minutes or to 400 minutes through increasing activity duration or intensity over a week. Our estimates can be interpreted as a weighted average of the effects of the different versions, weighted by the probability of each version naturally arising within the population.^{260,261} It should be noted that our estimates may not be generalizable to populations with different distributions of physical activity and TV viewing level. Results from the Australian National Health Surveys showed that the percentage of Australian adults with sufficient physical activity (i.e., ≥ 150 mins/week) remained low from 1989 to 2011 (39% in 1989 to 41% in 2011).²⁵⁹ The hypothetical interventions we considered may have a greater benefit on lowering mortality in the general population than in our sample where close to 60% can be classified as ‘sufficiently active’.

In conclusion, our findings suggest that sustained interventions on physical activity could lower all-cause mortality over a 13-year period, and that there might be limited gain from intervening on TV viewing time in a relatively healthy population.

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YY, AMH, PAD, BML, and DRE designed the study. YY performed the statistical analysis with support from EJW. YY, AMH, PAD, BML, and DRE drafted the manuscript. PAG, ELMB, NO, and DWD contributed to the data interpretation and provided critical feedback for each draft. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no relationship with companies or manufacturers who will benefit from the results of the present study. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Chapter 7 Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women

Objective 4 of the thesis is to estimate the effect of sustained midlife alcohol consumption on mortality in women. To address Objective 4, I analysed data from the Australian Longitudinal Study on Women's Health 1946-1951 birth cohort. This chapter presents the authors accepted version of the following manuscript in progress for publication:

Yi Yang, Allison M. Hodge, Brigid M. Lynch, Pierre-Antoine Dugué, Elizabeth J. Williamson, Harindra Jayasekara, Gita Mishra, Dallas R. English. Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women.

Supplementary material related to this publication is included in Appendix D.

Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women

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ABSTRACT

Background

No randomised controlled trial has evaluated the effect of long-term alcohol intake interventions on all-cause and cancer mortality. Associations reported in existing observational studies may have been biased due to selection of participants or time-varying confounding.

Methods

We emulated a target trial using data from the Australian Longitudinal Study on Women's Health 1946-51 birth cohort to estimate the effect of sustained alcohol intake interventions on all-cause and cancer mortality. We estimated the conventional association between baseline alcohol consumption and mortality using Cox regression, and the observational analogues to the per-protocol effect of sustained exposure using the parametric g-formula, to account for time-varying confounding and exposures over seven waves of data collection between 1998 and 2016.

Results

In 10,118 women, the cumulative risks for all-cause and cancer mortality were 5.6% (569 deaths, followed for 20 years) and 2.9% (292 deaths, followed for 18 years), respectively. For both all-cause and cancer mortality, the baseline analysis showed lower risk in low to moderate intake groups (up to 30g/day) and higher risk in the high intake group (>30 g/day) relative to abstainers. A similar relationship was observed for all-cause mortality in the per protocol analysis, with highest mortality in the zero and high (>30 g/day) intake groups. No level of alcohol consumption lowered cancer mortality in the per protocol analysis.

Conclusions

Our findings suggest that all-cause mortality would have been lower than observed if this cohort of women had moderate alcohol consumption, but cancer mortality would not. All-cause and cancer mortality would have been higher than observed had they consumed more than three standard drinks per day.

BACKGROUND

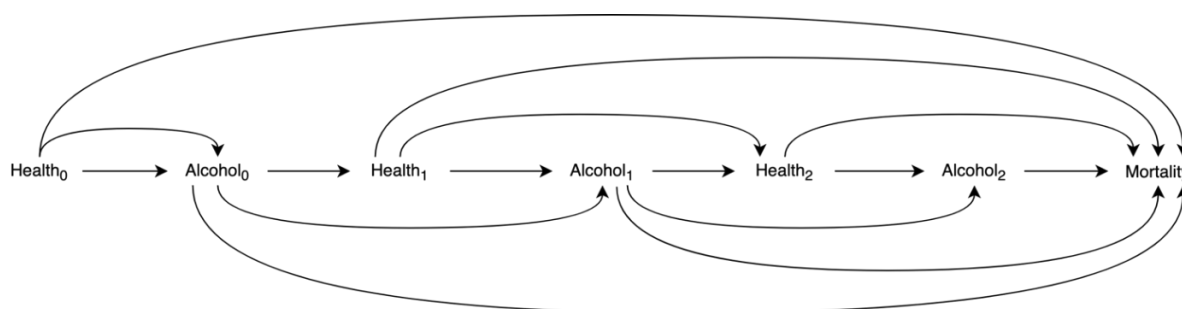
No randomised controlled trial has evaluated the effect of long-term alcohol interventions on all-cause or cancer mortality due to limited feasibility and ethical considerations. Evidence from observational studies consistently suggests that high doses of alcohol consumption are associated with increased mortality.^{262,263} For women aged 50 years and older, cancers accounted for an estimated 27% of total alcohol-attributable deaths in 2016.²⁶⁴ Some studies showed lower all-cause mortality for light or moderate consumption compared with abstention (i.e., a ‘J-shaped’ association),^{73,265} but criticisms remain that the J-shaped relationship is likely due to biases. For example, other characteristics of light to moderate drinkers such as higher socioeconomic status and physical activity may explain their lower mortality compared with abstainers. Furthermore, the reduced mortality in light to moderate drinkers might be partly due to the inclusion of former drinkers with abstainers in the reference category, as some former drinkers may have quit alcohol because of health problems (i.e., the ‘sick quitter’ effect).^{15,75,76}

Most cohort studies of alcohol and mortality measured alcohol consumption once, typically at study entry. It has been suggested that alcohol exposure over time should be the preferred measure, because consumption is likely to change over time and misclassification of true exposure could potentially bias the estimate of the effect on health outcomes.^{86,87} Although observational studies using time-varying alcohol data could provide more information on exposure over time, the data analysis poses other challenges. In studies collecting exposure data at multiple time points, selection of participants into the analysis would be affected by both the exposure (heavy drinkers are less likely to survive to later data collection waves) and the outcome (participants who died before the last data collection are not included). This would introduce selection bias that may underestimate the effect of alcohol drinking on mortality. Also, appropriate adjustment of time-varying confounding is necessary when alcohol consumption is measured repeatedly.¹⁸⁷ For example, as general health is a determinant of both alcohol drinking and mortality, some studies have excluded participants with prevalent baseline diseases to mitigate confounding due to reverse causation.²⁶⁶ However, conditioning only on baseline health status does not control for time-varying confounding from health deterioration during follow-up, and conditioning on time-updated health status would introduce bias by blocking part of the effect of alcohol on mortality that is mediated through post-baseline health status (Figure 7-1).

In this study, we aimed to estimate the effects of long-term alcohol consumption on all-cause and cancer mortality in middle-aged women, and to reduce selection bias and time-varying

confounding. Specifically, we emulated a target trial²⁶⁷ to estimate the effect of sustained hypothetical alcohol interventions initiated in midlife on 20-year all-cause mortality and 18-year cancer mortality using data from a prospective study of women.

Figure 7-1. Causal diagram: an example of time-varying confounding affected by prior exposure.



When estimating the effect of sustained alcohol exposure on risk of death in a regression model, not conditioning on time-varying general health will lead to unadjusted confounding. However, conditioning on time-varying general health will block some of the causal pathways from alcohol to death that are mediated to post-baseline general health.

METHODS

The cohort

The Australian Longitudinal Study on Women’s Health (ALSWH) is a population-based prospective cohort study examining the health of Australian women. Three nationally representative cohorts of women (born in 1973-78, 1946-51, 1921-26, respectively) were recruited in 1996. Data used in the present study were from the 1946-51 birth cohort. In 1996, participants were randomly selected from women registered in the Australian national health insurance scheme database, Medicare. Approximately 53-56% of women invited completed a questionnaire about their lifestyle and health (n=13,714). Further waves of data were collected every 2 to 3 years with paper or web-based questionnaires in 1998 (n=12,338), 2001 (n=11,226), 2004 (n=10,905), 2007 (n=10,638), 2010 (n=10,011), 2013 (n=9,151) and 2016 (n=8,622), respectively. Details about the cohort have previously been reported.^{192,193} In the present study, we used the 1998 wave as time zero (referred to as baseline hereafter) to be able to adjust for pre-baseline confounders. Women who did not return the 1998 questionnaire or had unknown death date (n=1,377) were excluded. To reduce baseline confounding from ill health, we also excluded participants who reported having “fair” or “poor” general health (as opposed to “good”, “very good”, or “excellent” general health) at baseline (i.e., in 1998)

(n=1,508), had been diagnosed with or treated for cancer before baseline (n=613), or had missing information for subjective general health or cancer diagnosis and treatment at baseline (n=98). These exclusions left 10,118 women eligible for analysis. A timeline of the data collection waves, and exclusions made is presented in Supplementary Figure 7-1.

Alcohol data

Alcohol data were obtained from two questions about the participants' usual intake: "How often do you usually drink alcoholic beverages?", and "On a day when you drink alcoholic beverages, how many drinks do you usually have?". The type of beverages consumed was not asked. Therefore, daily pure alcohol intake could only be approximated. The frequency and quantity of alcohol consumption approximated from each questionnaire response are presented in Box 7-1. Each reported alcoholic drink was assumed to be 1.5 Australian standard drinks. Each standard drink contains 10 grams of alcohol.¹⁹⁷ For responses reporting a range of frequencies or quantities, the mid-point was used as a multiplying factor.¹⁹⁹ Daily alcohol intake (in grams of ethanol) was calculated as follows:

$$\text{Alcohol intake (g/day)} = F \times Q \times 10 \text{ (g/standard drink)} \div 7 \text{ (days/week)},$$

where F is the weekly frequency of alcohol consumption (days/week), and Q is the number of standard drinks on a day of drinking.

Box 7-1. Frequency and quantity of alcohol consumption approximated for each questionnaire response

Frequency Question: How often do you usually drink alcoholic beverages?		Quantity Question: On a day when you drink alcoholic beverages, how many drinks do you usually have?		
Response	F (days/week) *	Response	Approximate drinks*	Q (Numbers of standard drink/day)^
Never or former	0	I don't drink	0	0
I rarely drink	0.25	1 or 2 drinks	1.5	2.25
<1 /week	0.5	3 or 4 drinks	3.5	5.25
1 or 2 days/week	1.5	5 to 8 drinks	6.5	9.75
3 or 4 days	3.5	≥ 9 drinks	9	13.5
5 or 6 days	5.5			
Every day	7			

F: Weekly frequency; Q: standard drinks on a day of drinking. * For responses reporting a range, the mid-point is used as a multiplying factor. ^ 1 reported drink $\approx$ 1.5 Australian standard drink

In 2001 and 2013, individuals completed a separate food frequency questionnaire (FFQ), which included questions about consumption of specific types of alcoholic beverages. The amount of each alcoholic beverage (beer, wine, spirits) was multiplied by the daily equivalent frequency and alcohol content to calculate the daily alcohol intake.¹⁹⁵ As the 2001 questionnaire did not include the frequency and quantity questions, we calibrated the daily alcohol intake calculated from the FFQ using regression calibration based on the 2013 data (where alcohol questions were asked in both the main questionnaire and the FFQ): for current drinkers in 2001, *alcohol intake* = $\alpha + \lambda * \text{FFQ intake}$, where α and λ were estimated from linear regression of the 2013 questionnaire-estimated intake against 2013 FFQ-estimated intake.²⁰⁰

Mortality data

Deaths were ascertained through record linkage to the National Death Index at the Australian Institute of Health and Welfare. Underlying cause of death was defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10, codes C00-C97 for cancer deaths). All-cause mortality data were complete to 31 December 2018; cause of death data were complete to 31 December 2016.

Target trial emulation

Box 7-2 describes the emulation of a target trial that aims to estimate the effect of sustained alcohol interventions on 20-year all-cause mortality and 18-year cancer mortality among Australian women aged 47-52 years at baseline.^{189,267,268}

Statistical analysis

Baseline analysis. We fit Cox regression with age as the time scale to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cancer mortality associated with baseline alcohol intake, regardless of whether the individuals continued with the same intake after baseline. Follow-up began at the return date of the baseline questionnaire, and ended at date of death, or date when mortality data were complete (31 December 2018 for all-cause mortality; 31 December 2016 for cancer mortality), whichever came first. The models included the following time-fixed covariates measured pre-baseline (in 1996): country of birth, highest educational qualification, alcohol consumption levels in late teens, twenties, and thirties, ever smoked 100 or more cigarettes, self-reported history of depression, heart disease, and diabetes. We also included the following confounders (also measured pre-baseline to establish a clear temporal ordering of the confounders and exposure ²⁶⁹): living in most socioeconomically disadvantaged areas (defined using an Australian area-based index of relative socioeconomic

disadvantage, IRSD ²²⁰), marital status, physical activity level, daily number of cigarettes, body mass index (BMI), and poor or fair subjective general health before baseline of this analysis (i.e., in 1996) (see Supplementary Table 7-1 for units and categories of these variables). Daily vegetable intake was not available in 1996 and 1998.

We investigated the proportional hazards assumption by including interaction terms between time and the covariates. In the case of evidence for a violation ($p < 0.05$), the interaction term for the corresponding variable remained in the model.

Observational analogue to per-protocol analysis. We used the parametric g-formula to estimate the per-protocol effect of the alcohol interventions listed in Box 7-2, i.e., the effect on all-cause and cancer mortality had all women followed the assigned intervention. The parametric g-formula is a generalisation of standardisation to time-varying exposures and confounders that handles time-varying confounding appropriately when the time-varying confounders are affected by prior alcohol consumption.¹⁸⁷

We fit parametric models for the conditional distribution of the following time-varying variables from each wave: alcohol intake, living in most socioeconomically disadvantaged areas, marital status, physical activity level, daily number of cigarettes, daily vegetable intake, BMI, diagnoses or treatment of depression or anxiety since last survey, diagnoses or treatment of comorbidities since last survey (cancer, heart diseases, hypertension, or diabetes), and participants' subjective general health. To ensure correct temporal ordering of confounders and exposure, we used time-varying confounder data collected one wave prior to exposure measurement to ensure they were not intermediate variables.²⁶⁹ All models also included time-fixed confounders (age at baseline, country of birth, highest educational qualification, and alcohol intake in late teens, 20s and 30s, pre-baseline history of depression, heart disease, hypertension, or diabetes), pre-baseline and the most recent value of the time-varying covariates. A pooled-over-interval logistic model was fit to estimate the conditional discrete-time hazard of death for each time interval.^{270,271} For cancer mortality, death due to other causes was treated as a competing event. A logistic model was fit to estimate the conditional discrete-time hazard of death due to other causes at each time interval, which was necessary to compute the sub-distribution cumulative incidence function (See Supplementary Table 7-1 for units and categories of covariates and details of parametric models). We also assessed the robustness of our estimates to various covariate orders when modelling the joint distribution of time-varying covariates.

We then used the above models to predict the outcome had the alcohol intake been set to a value determined by the interventions listed in Box 7-2 using a Monte Carlo sample of 20,000 women drawn with replacement from the existing cohort. For comparison, we calculated risk ratios (RR) and risk differences (RD) for each intervention and scenario, using the ‘no intervention’ as the reference category. Nonparametric bootstrapping (500 resamples) was used to obtain 95% CIs.

Imputation of missing data

Multiple imputation using chained equation (MICE)²⁵³ was used to impute missing data due to incomplete questionnaire responses or non-responses from women who were alive at a wave. We included all variables to be used in the parametric g-formula and the Cox models, and auxiliary variables that were correlated (Pearson’s $r > 0.6$) with the variables that had missing data. After taking into account their responses at other waves and their fully observed mortality status, we assumed the data were missing at random, i.e., the probability of data being missing did not depend on the unobserved data, conditional on the observed data.²⁵³ We used 30 imputations for all analyses. In the parametric g-formula analyses, point estimates for each intervention were averaged over all imputed datasets; bootstrap samples were drawn for each imputed data set to estimate the standard errors; 95% CIs were calculated using Rubin’s rules.²⁵⁵

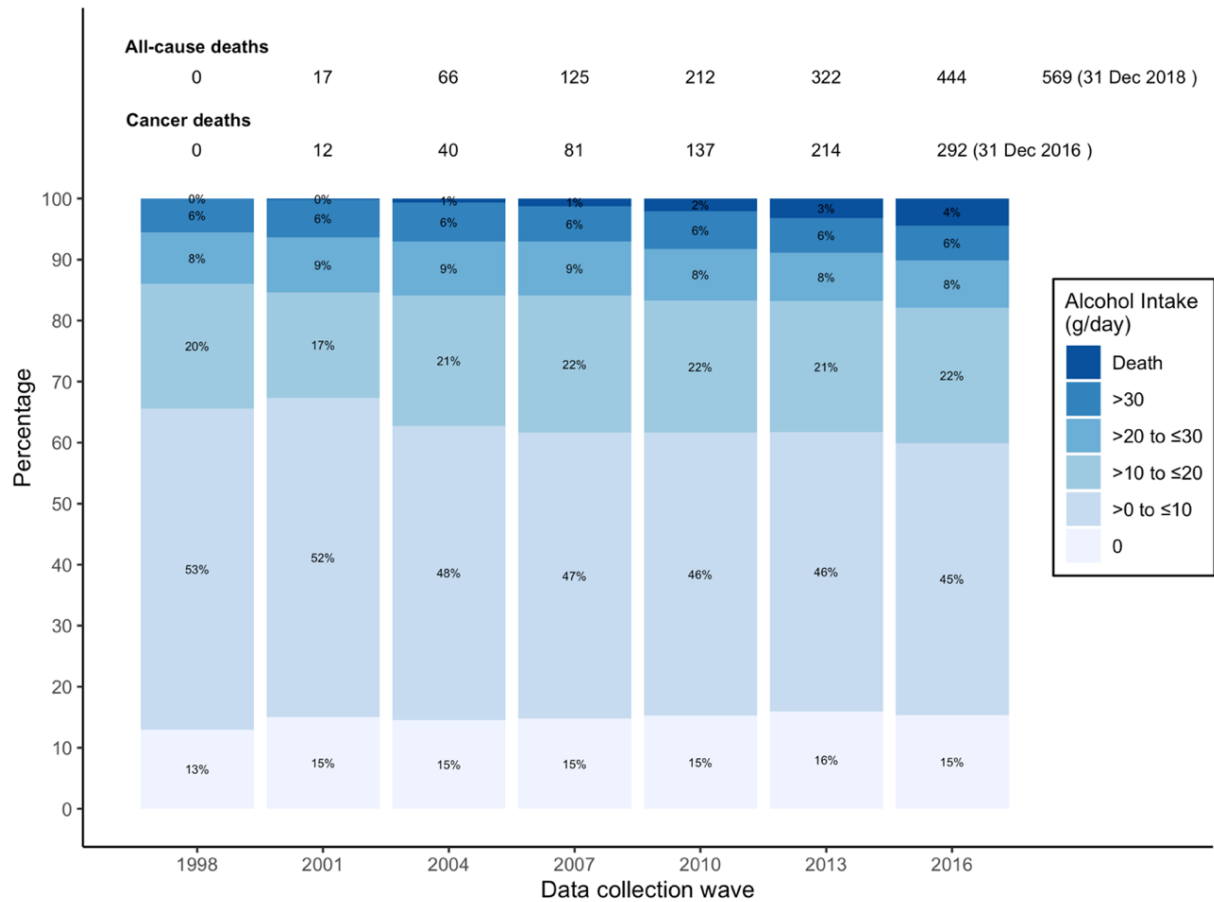
The parametric g-formula analysis was conducted using SAS 9.4 (the SAS GFORMULA 3.0 macro and documentation are available at <https://www.hsph.harvard.edu/causal/software>), other analyses were conducted using Stata 14.2.

RESULTS

Baseline characteristics of the 10,118 eligible women by alcohol intake categories are presented in Table 7-1. The proportion of current smokers increased as the intake increased. Physical activity was lowest in the two extremes of intake (0 g/day and >30 g/day). Mean BMI was lower and subjective general health was better in “>10 to 20 g/day” and “>20 to 30 g/day” groups than other alcohol categories. The abstainer (0 g/day) and the “>0 to 10 g/day” groups had higher percentages of women without a formal educational qualification and living in the most socioeconomically disadvantaged areas than higher intake groups. The “>10 to 20 g/day” and “>20 to 30 g/day” groups had proportionally fewer women living in the most

socioeconomically disadvantaged areas, and more women who had a diploma or higher qualification, and were more physically active. The “>30g/day” group had proportionally more former and current smokers, and higher mean number of cigarettes consumed by current smokers than other groups. This group also had higher percentages of women with a history of depression, anxiety, or hypertension.

Figure 7-2. Alcohol intake and cumulative number of deaths over time in the 10,118 eligible women



This figure is based on multiply imputed dataset of the 10,118 women who were eligible at baseline. Percentages are averaged over 30 imputations.

Figure 7-2 gives an overview of the alcohol intake distributions in the 10,118 women over time under no intervention, and the cumulative number of deaths at each wave. Percentage of abstainers increased from 13% in baseline (1998) to 15% in 2001 and remained relatively stable afterwards. More than half (53%) of the women were in the “>0 to 10 g/day” group at baseline. This number gradually decreased over time to 45% in 2016. The percentage of women in the “>10 to 20 g/day” group remained around 20-22% except for the year 2001 when it was 17%.

The percentages of women in the “>20 to 30 g/day” and “>30 g/day” groups were relatively stable from baseline to 2016 (8 to 9 %, and 6%, respectively).

During an average of 20 years of follow-up, 569 women died; and during an average of 18 years of follow-up, 292 died from cancer. A higher proportion of women who died reported not drinking, being physically inactive, currently smoking, and having comorbidities at baseline than those who were alive at the end of follow-up (Supplementary Table 7-2).

Table 7-2 shows HRs for all-cause and cancer mortality in relation to baseline alcohol intake, regardless of whether women maintained the same intake afterwards. Although the HRs were estimated imprecisely with wide 95% CIs, the point estimates suggested that baseline alcohol intakes up to 30 g/day were associated with reduced all-cause mortality compared with abstinence, while consumption of more than 30g/day was associated with higher all-cause mortality. Similarly, the point estimates suggested that cancer mortality was lower in women with intakes up to 30g/day with wide CIs.

Figure 7-3 shows the 20-year all-cause mortality, and Figure 7-4 shows the 18-year cancer mortality had the women followed the assigned alcohol interventions. The estimated risks under no intervention were 56 per 1000 women and 28 per 1000 women for all-cause and cancer mortality, respectively, which closely reproduced the observed risks of 56 and 29 per 1000 women.

As shown in Figure 7-3, all-cause mortality was lowest under interventions of moderate drinking (“>10 to 20g/day” and “>20 to 30g/day”). We observed 17-18% lower all-cause mortality under interventions >10 to 20g/day (RR=0.83, 95% CI 0.68 to 0.98; RD=-10, -18 to -1 per 1000 women) and >20 to 30g/day (RR=0.82, 95% CI 0.63 to 1.02; RD=-10, -21 to 1 per 1000 women) compared with no intervention, for which the average percentages intervened on was also highest (71% and 83%, respectively). The sustained low drinking intervention (“>0 to 10g/day”, 28% intervened on) showed no difference in risk compared with the no intervention scenario. The estimated all-cause mortality under the sustained non-drinking intervention and the “>30g/day” intervention were higher than under no intervention, with wide CIs (RR=1.14, 95% CI 0.75 to 1.53; RD=8, -14 to 29 per 1000 women; RR=1.13, 95% CI 0.83 to 1.42; RD=7, -10 to 24 per 1000 women). Reducing drinking to ≤ 20 g/day if higher slightly lowered all-cause mortality compared with no intervention (RR=0.94, 0.89 to 0.99; RD=-3, -6 to 0 per 1000 women), with an average of 10% intervened on.

The point estimate for cancer mortality was slightly lower under the “>10 to 20g/day” intervention (RR=0.90, 0.70 to 1.10; RD=-3, -9 to 3 per 1000 women) and marginally higher in the “>30g/day” intervention (RR=1.15, 0.77 to 1.53; RD=4, -7 to 15 per 1000 women) than in the no intervention scenario, both with wide CIs (Figure 7-4). Other interventions appeared to have no effect on cancer mortality. The estimates in Figure 7-3 and Figure 7-4 were robust to different modelling orders of covariates (Supplementary Table 7-3).

DISCUSSION

Using data from the ALSWH 1946-51 birth cohort, we emulated a target trial to estimate the effect of sustained alcohol interventions initiated in midlife on 20-year all-cause mortality and 18-year cancer mortality in women. Our baseline analysis using Cox regression showed weak evidence for lower mortality with low to moderate alcohol intake (up to 30g/day) and higher mortality with intakes above 30 g/day relative to abstinence. Although the results from the parametric g-formula (risk differences and ratios) are not directly comparable to those from the Cox regression (hazard ratios), a similar relationship was observed for all-cause mortality in the per protocol analysis with slightly more pronounced lower mortality seen for intakes of >10 to 30g/day relative to the no intervention scenario. This inverse relationship with low to moderate intake was not present in the model assessing cancer mortality while evidence was also weak for higher mortality with intakes above 30 g/day in the per-protocol analysis.

The strengths of our study include the use of data from a prospective cohort study with regular measurements of alcohol intake and potential confounders. We emulated a target trial on sustained alcohol interventions and mortality for a situation where randomised trials are infeasible. Using the parametric g-formula, we could also better adjust for time-varying confounding when estimating the per-protocol effect of sustained alcohol intervention, which provided estimates that are easy to interpret and directly relevant for guiding policy making. Our study also contributed to the scarce literature on long-term alcohol consumption and mortality in women.^{80,272}

Several limitations of our study need to be considered before interpreting the results. A major limitation was that the alcohol questionnaire only provided a response option for former drinking from 2007 onwards, therefore, we were unable to disentangle a mortality effect of alcohol cessation from lifetime abstinence. This may partly explain the elevated mortality in the abstinence group relative to moderate drinking for the baseline (all-cause and cancer

mortality) and per-protocol analysis (all-cause mortality). In the per-protocol analysis, we avoided using the abstention group as the reference and compared risks under other interventions to a “no intervention” scenario.

Another limitation relates to potential residual confounding. Health status, including self-rated general health and development of serious health conditions, is a strong predictor for both alcohol cessation and mortality.⁷⁷ In the per-protocol analysis, we cannot rule out the possibility of residual confounding from participants’ health deterioration, which may not be fully captured by self-rated general health and comorbidities measured every two to three years. A simulation study showed that in a yearly interval-measurement scenario, as the strength of confounding increases, the true effect of the exposure could not be fully recovered even when using g-methods that appropriately adjust for time-varying confounding.²⁷³ Nevertheless, the study showed that results were less biased compared with ignoring time-varying confounding completely. To adequately address the ‘sick-quitting’ problem, studies need to collect data on reasons for ceasing or reducing alcohol consumption.

Although the parametric g-formula allows estimation of per-protocol effects without introducing biases of conditioning on a common effect or a mediator as a conventional regression analysis would, it does not eliminate other potential biases. Like other analyses of observational data, we cannot exclude the possibility of unmeasured confounding despite careful adjustment of potential confounders available in the data to approximate randomisation. We were also limited by the reliance on self-reported alcohol and confounder variables, which may have introduced misclassification of the exposure and residual confounding due to imperfect measurements of confounders. Specifically, at most waves, participants only reported frequency and quantity of drinking alcoholic beverages without information on the type of beverage consumed. Therefore, daily pure alcohol intake could only be approximated. Also, validity of estimates from the parametric g-formula relied on correct model specifications. The fact that we were able to closely reproduce the observed risks of death under the “no intervention” scenario (a necessary condition for no overall model misspecification) provided reassurance that our model specification was adequate overall.²⁷⁴ Finally, the imputation of missing data relied on the missing-at-random assumption. We believed that the key drivers of missingness were likely captured in the data included in the imputation models.

A meta-analysis of observational studies on alcohol consumption over adulthood and risk of death found a J-shaped relationship between alcohol intake over time and all-cause mortality in men, and found studies including women were scarce.⁸⁰ A study of middle-aged adults in

the Melbourne Collaborative Cohort Study²⁵² observed a consistent J-shaped relationship between alcohol intake over mid-adulthood and all-cause mortality in women, i.e., lower mortality at low intake level (<10 g/day of lifetime average) and elevated mortality at higher intake levels relative to zero intake. Similarly, in the European Prospective Investigation into Cancer and Nutrition (EPIC),²⁷⁵ female never drinkers and heavy drinkers (≥ 30 g/day lifetime average) had higher total mortality than light to moderate drinkers (0.1 to 4.9 g/day lifetime average); the HRs were 1.26 (1.18 to 1.35) for never drinkers and 1.27 (1.13 to 1.43) for heavy drinkers. Heavy drinking was also associated with a higher risk of death due to alcohol related cancers in women, including cancers of the upper aerodigestive tract, liver, colorectum and female breast (HR=1.49, 1.07 to 2.06). Findings from a study of older adults in the US (The Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial) reported a consistent J-shaped association between lifetime alcohol consumption and mortality, with intakes below one drink per day being associated with the lowest total mortality.²⁷⁶ However, these studies using lifetime average intake do not provide information on patterns of change in consumption, for example, whether the individuals increased, decreased, or maintained their intake over time, and importantly, reasons for any changes.

Some studies of women have assessed mortality effects of changes in alcohol drinking. A study of adults in California found that women who quit drinking had higher all-cause mortality than women who continued to drink over 10 years (HR=1.72, 1.11 to 2.66).⁹⁰ A study of a cohort of young Swedish women reported that compared with maintaining a low alcohol consumption (<5g/day), abstinence (HR=1.53, 1.20 to 1.96) and quitting (HR=1.49, 1.10 to 2.02) between two waves were associated with increased overall mortality, while maintaining a higher intake ≥ 5 g/day was not associated with increased mortality.²⁷² However, these estimates could be biased due to lack of, or inappropriate adjustment for time-varying confounding. For example, the Alameda study did not adjust for time-varying confounders, while the Swedish study adjusted for confounders measured at follow-up visit which could also be mediators of any effect of alcohol on mortality.

In cohort studies of lifetime alcohol consumption or of changes in consumption over time, follow-up is often set after the start of exposure. For example, in the PLCO Cancer Screening Trial study²⁷⁶, follow-up started at the time when lifetime alcohol exposure (from age 18 to 55+ years) was recalled, instead of the time when the exposure of interest started. The left-truncation of follow-up would generally bias the estimate because such analyses were restricted to people who survived until the truncation date.²⁶⁸ Using the target trial approach, we were

able to align start of follow-up with start of the exposure of interest (i.e., alcohol intervention initiated midlife, Box 7-2).

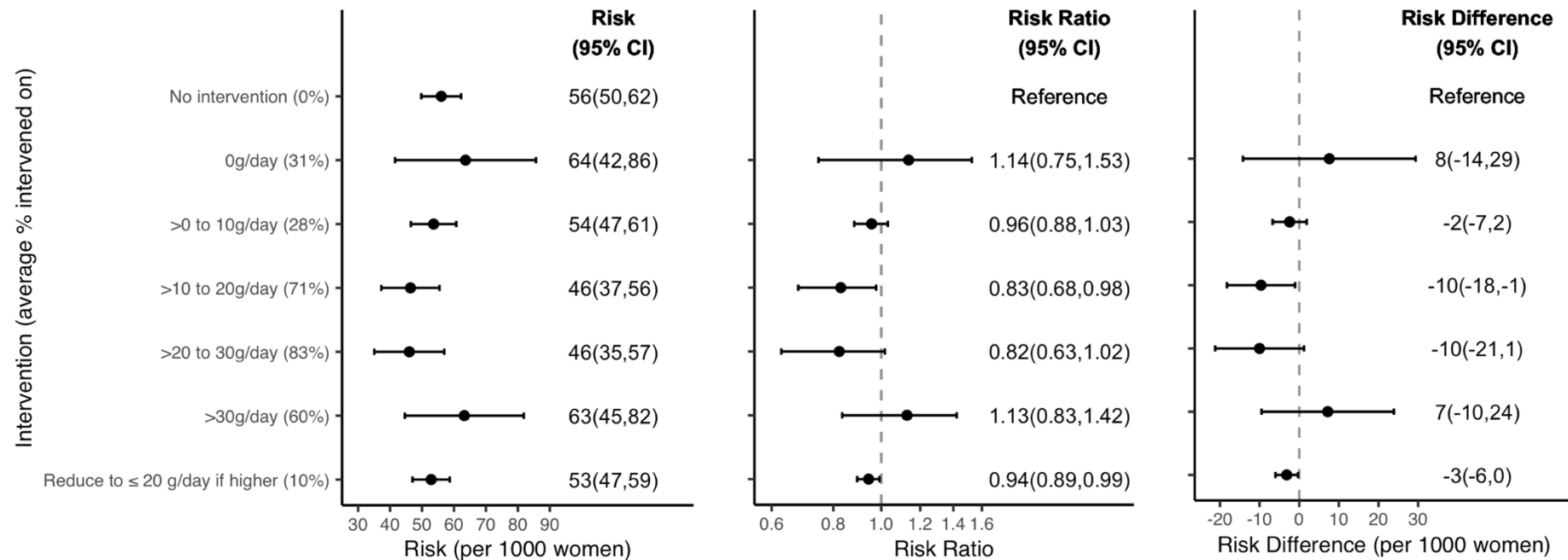
Our per-protocol analysis showed limited improvement in all-cause and cancer mortality in this cohort of women under an intervention of reducing alcohol consumption to no more than two standard drinks if the observed consumption was higher. The Australian National Health Surveys showed that only about 10% of women aged between 45 and 64 consumed more than two standard drinks per day in 2017/18, which was lower than the 14-15% in ALSWH 1946-51 birth cohort.²⁷⁷ Therefore, the effect of such intervention may be even smaller for women in this age range in the general population.

In conclusion, our findings suggest that all-cause mortality would have been slightly lower than observed if this cohort of women had moderate alcohol consumption, but cancer mortality would not. All-cause and cancer mortality over the long term in this cohort would have been higher had they consumed more than three standard drinks per day. Methodological challenges will need to be addressed in future studies to provide greater insight for understanding mortality effects of long-term alcohol exposure.

ACKNOWLEDGEMENTS

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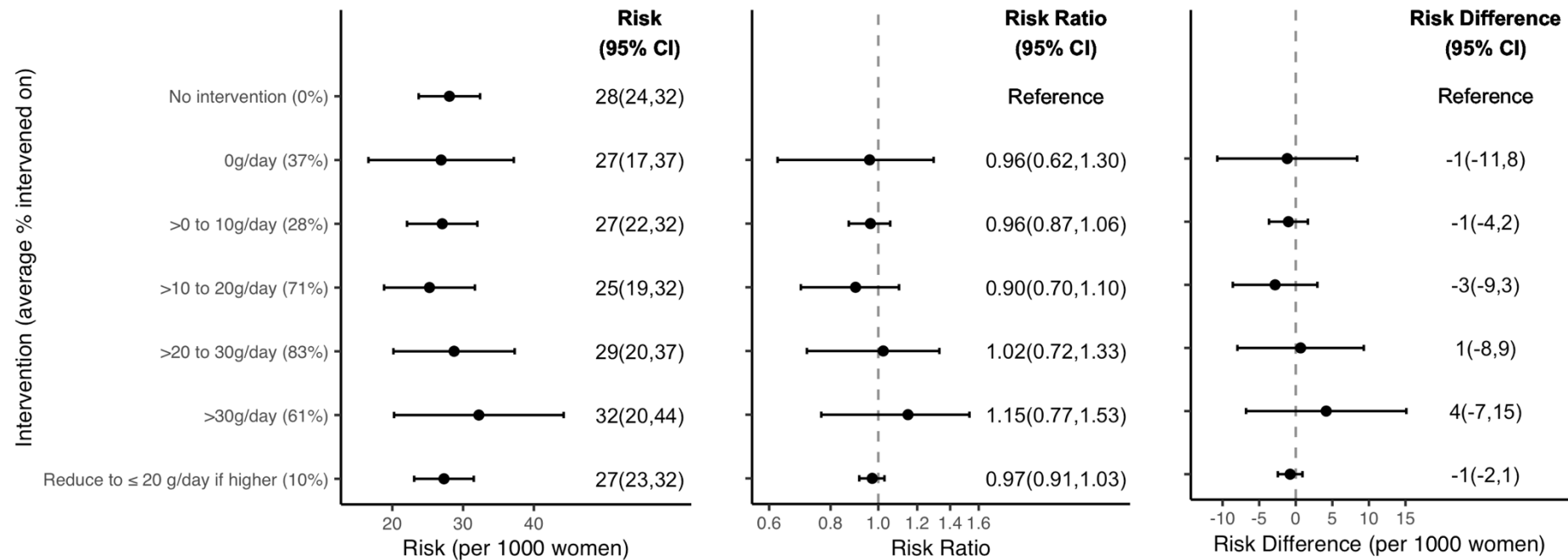
Figure 7-3. Estimated all-cause mortality over 20 years had the women followed the hypothetical alcohol interventions (observational analogue to per-protocol analysis of the target trial)



Observed risk was 56 per 1000 women. Average % intervened on was averaged over all waves.

Adjusted for the following time-fixed confounders: baseline age, country of birth, highest educational qualification, alcohol intake in late teens, 20s and 30s, ever diagnosed with depression, heart disease, hypertension, or diabetes before baseline, and the following time-varying confounders: living in most socioeconomically disadvantaged areas, marital status, physical activity level, daily number of cigarettes, daily vegetable intake, BMI, diagnoses or treatment of depression or anxiety since last survey, diagnoses or treatment of comorbidities since last survey (cancer, heart diseases, hypertension, or diabetes), and participants' subjective general health.

Figure 7-4. Estimated cancer mortality over 18 years had the women followed the hypothetical alcohol interventions (observational analogue to per-protocol analysis of the target trial)



Observed risk was 29 per 1000 women. Average % intervened on was averaged over all waves.

Adjusted for the following time-fixed confounders: baseline age, country of birth, highest educational qualification, alcohol intake in late teens, 20s and 30s, ever diagnosed with depression, heart disease, hypertension, or diabetes before baseline, and the following time-varying confounders: living in most socioeconomically disadvantaged areas, marital status, physical activity level, daily number of cigarettes, daily vegetable intake, BMI, diagnoses or treatment of depression or anxiety since last survey, diagnoses or treatment of comorbidities since last survey (cancer, heart diseases, hypertension, or diabetes), and participants' subjective general health.

Box 7-2. Target trial emulation

Protocol component	Target trial specification	Emulation using data from ALSWH 1946-51 cohort
Aim	To estimate the effect of sustained alcohol interventions on 20-year all-cause mortality and 18-year cancer mortality in Australian women aged 47-52 years.	Same.
Eligibility	Australian women aged 47-52 years in 1998.	Same.
Alcohol interventions	Participants are randomly assigned to have the following intake levels from throughout the follow-up period: 0 g/day >0 to 10 g/day >10 to 20 g/day >20 to 30 g/day > 30 g/day - Reduce drinking to at most 20g/day if currently drinking more than 20g/day	Same.
Assignment procedure	Randomisation to one of the alcohol drinking interventions.	To emulate the random assignment of interventions, we adjusted for confounders required to ensure exchangeability of the groups (Supplementary Table 7-1).
Start of follow-up	Time of randomisation.	Return date of the 1998 questionnaire.
End of follow-up	Death, or administrative end of follow-up, whichever came first.	Same. Administrative end of follow-up was the date when mortality data were complete: All-cause mortality data were complete to 31 December 2018; cancer mortality data were complete to 31 December 2016.
Outcome	Deaths due to any cause within 20 years of intervention assignment; deaths due to cancer within 18 years of intervention assignment.	Deaths due to any cause within 20 years after baseline; deaths due to cancer within 18 years after baseline.
Causal contrast of interest	Per-protocol effect, i.e., Effect that would have been observed had all women adhered to their assigned intervention over the follow-up. Intention-to-treat effect, i.e., effect of being assigned to an alcohol intervention.	Observational analogues to the intention-to-treat and the per-protocol effect.
Statistical analysis	Intention-to-treat analysis Estimation can be done through comparing the outcomes of the groups assigned to each intervention. Per-protocol analysis Estimation of the per-protocol effect requires adjustment for baseline and post-baseline prognostic factors associated with adherence to the assigned intervention. Because post-baseline prognostic factors associated with subsequent adherence to the assigned intervention may be affected by prior adherence, g-methods are required.²¹	Baseline analysis Intention-to-treat analysis is rarely possible in observational studies. A close analogue of the intention-to-treat effect is a comparison of baseline values of the different intervention strategies, assuming adequate adjustment for baseline confounders. Per-protocol analysis Adjustment for baseline and post-baseline confounding is necessary when exposure to alcohol is sustained over time. Because post-baseline confounders are affected by prior exposure, g-methods are required.

Table 7-1. Baseline characteristics of eligible women, by baseline alcohol intake

Characteristics of women	Baseline alcohol intake (g/day)				
	0g/day N=1176	>0 to 10 g/day N=4815	>10 to 20 g/day N=1926	>20 to 30 g/day N=799	>30 g/day N=528
Born in Australia, N (%)	875(75.4)	3640(76.2)	1496(78.3)	615(77.8)	413(79.0)
Married or de facto, N(%)	994(85.1)	3962(82.8)	1643(85.8)	693(87.0)	437(83.4)
Highest educational qualification, N (%)					
No formal qualification	261(22.4)	766(16.0)	188(9.8)	100(12.6)	73(14.0)
School certificate	582(49.9)	2411(50.4)	875(45.8)	385(48.6)	256(48.9)
Diploma/University/Higher degree	324(27.8)	1603(33.5)	849(44.4)	307(38.8)	194(37.1)
Most disadvantaged quartile, Area-based Index of Relative Socio-Economic Disadvantage, N(%)	308(26.2)	1179(24.5)	389(20.2)	163(20.4)	121(22.9)
Smoking status, N(%)					
Never	844(72.0)	2911(60.7)	1031(53.7)	338(42.4)	160(30.4)
Former	187(15.9)	1198(25.0)	632(32.9)	283(35.5)	197(37.4)
Current	142(12.1)	684(14.3)	256(13.3)	176(22.1)	170(32.3)
Cigarettes per day for current smoker, n/day, median (IQR)	20(15,25)	20(12,25)	18(10,20)	20(10,25)	25(15,30)
Physical activity, N(%)					
Very low (0 to <33.3 METmin/week)	224(19.9)	738(15.8)	235(12.4)	112(14.4)	100(19.6)
Low (33.3 to <500 METmin/wk)	318(28.3)	1389(29.8)	483(25.5)	192(24.6)	141(27.6)
Moderate (500 to <1000 METmin/wk)	248(22.1)	1125(24.2)	476(25.1)	192(24.6)	113(22.1)
High (>=1000 METmin/wk)	333(29.7)	1405(30.2)	702(37.0)	283(36.3)	157(30.7)
Body mass index, kg/m ² , mean(SD)	27(6.0)	27(5.3)	25(4.2)	25(4.2)	26(4.6)
Subjective general health, N(%)					
Excellent	149(12.7)	645(13.4)	362(18.8)	141(17.6)	65(12.3)
Very good	445(37.8)	2044(42.5)	907(47.1)	376(47.1)	238(45.1)
Good	582(49.5)	2126(44.2)	657(34.1)	282(35.3)	225(42.6)
Ever had the following conditions, N(%)					
Depression or anxiety	111(9.4)	475(9.9)	183(9.5)	83(10.4)	67(12.7)
Heart diseases	10(0.9)	18(0.4)	12(0.6)	6(0.8)	2(0.4)
Hypertension	103(8.8)	387(8.0)	141(7.3)	56(7.0)	67(12.7)
Diabetes	21(1.8)	40(0.8)	8(0.4)	5(0.6)	1(0.2)

This table uses the data before multiple imputation. Abbreviations: N, numbers; SD, standard deviation; IQR, inter-quartile range; MET, metabolic equivalent.

Table 7-2. Hazard ratios for all-cause and cancer mortality in relation to baseline alcohol intake, regardless of whether individuals continued on the same intake level after baseline (baseline analysis of the target trial)

Baseline daily alcohol intake (g/day)	All-cause mortality			Cancer mortality		
	Person-years	Deaths^	Hazard Ratio (95% CI)	Person-years	Deaths^	Hazard Ratio (95% CI)
0	23710	86	1.00	21499	45	1.00
>0 to 10	97775	286	0.88 (0.65, 1.18)	88599	147	0.82 (0.55, 1.22)
>10 to 20	39218	97	0.84 (0.59, 1.21)	35525	52	0.81 (0.49, 1.32)
>20 to 30	16236	44	0.85 (0.56, 1.31)	14711	23	0.81 (0.45, 1.45)
>30	10536	53	1.45 (0.94, 2.24)	9570	25	1.33 (0.72, 2.45)

Age was the timescale, adjusted for country of birth, highest educational qualification, alcohol consumption levels in late teens, 20s, and 30s, ever smoked 100 or more cigarettes, self-reported history of depression, heart disease, and diabetes, and the following covariates measured in 1996: living in most socioeconomically disadvantaged areas, marital status, physical activity level, daily number of cigarettes, BMI, and poor or fair subjective general. Daily vegetable intake was not available in 1996 and 1998. ^ number of deaths in each category was averaged across 30 imputations because some death cases had missing alcohol data, and imputed alcohol intake values differ slightly in each imputation. Number of deaths (averaged total, n=566) did not equal the observed number of deaths (n=569) due to rounding.

Chapter 8 Discussion

To date, the evidence relating lifestyle-related exposures to mortality has largely been derived from studies examining exposures measured at one time point. There has been limited research examining exposures over the long term, despite many cohort studies having collected information on exposures and confounders at multiple time points. This thesis consists of four studies: a systematic review of evidence from mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour, and three studies examining the mortality effects of long-term adulthood BMI, physical activity, TV viewing, and midlife alcohol consumption, using repeated waves of data from three Australian cohort studies. (Table 8-1, an overview of studies). This chapter summarises the main findings from each study. The findings are interpreted and discussed, considering the studies' strengths and limitations. This chapter also discusses how my findings contribute to the knowledge base, the implications of the findings, and opportunities for future research.

Table 8-1 An overview of studies in this thesis

Study	Objective of the thesis	Study population	Exposure type	Mortality outcome examined
1	Summarise the evidence from mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour	Systematic review of the literature	Adulthood physical activity and sedentary behaviour, repeatedly assessed over time	All-cause, cardiovascular disease, and cancer mortality
2	Examine BMI trajectories over adulthood and their effect on mortality	Melbourne Collaborative Cohort Study (MCCS)	Adulthood BMI, categorised using group-based trajectory models	All-cause, cardiovascular disease, and obesity-related cancer mortality
3	Estimate the effects of physical activity and sedentary behaviour over adulthood on mortality	Australian Diabetes, Obesity and Lifestyle (AusDiab) Study	Hypothetical interventions on adulthood leisure-time physical activity and TV viewing	All-cause mortality
4	Estimate the effect of midlife alcohol consumption on mortality in women.	Australian Longitudinal Study on Women's Health (ALSWH) 1946-1951 birth cohort	Hypothetical interventions on midlife alcohol consumption	All-cause and cancer mortality

8.1 Summary of main findings

Study 1: Evidence from mortality studies that repeatedly assessed adulthood physical activity and sedentary behaviour

The systematic review provided an up-to-date summary of studies that used repeatedly assessed data on physical activity and sedentary behaviour and examined their effects on all-cause or all-cause mortality. The systematic review summarised the study findings and critically appraised the analytic methods used in these studies. Almost all studies were cohort studies that collected data prospectively. The most common way to treat repeatedly measured exposures was to categorise them into a summary variable such as change or persistence between two time points, or average or trajectory over more time points. The most widely used statistical analysis method was Cox regression with a time-fixed exposure history, or with time-varying covariates. Most of the identified studies were subject to moderate to serious risk of bias, mainly arising from inadequate adjustment of time-varying confounding, selection of participants affected by post-baseline vital status, questionnaire-based exposure assessment, and departure from baseline exposure during long passive follow-up periods. The findings suggest that maintaining a more physically active and less sedentary lifestyle over adulthood reduces all-cause and cardiovascular mortality moderately. Few studies examined cancer mortality. These findings need to be interpreted cautiously considering heterogeneity in methods and potential sources of bias. Additional studies using methodologically sound analysis of repeatedly measured exposure data would help strengthen the evidence on the health benefits of a more physically active and less sedentary lifestyle over the course of adulthood.

Study 2: Adulthood BMI trajectories and mortality in the Melbourne Collaborative Cohort Study (MCCS)

Six quadratic BMI trajectories were identified in these adults in metropolitan Melbourne. Most participants started with normal BMI in early adulthood and maintained a higher-normal BMI throughout adulthood or gained weight from higher-normal to overweight. A relatively small proportion of people developed obesity in mid to late life.

Participants following a trajectory of stable higher-normal BMI throughout adulthood had the lowest mortality relative to other trajectories. Relative to the “stable lower-normal trajectory”, participants who were obese across the midlife had the most elevated all-cause mortality, even if they had normal BMI at a younger age (9% to 31% higher), as did those who had prolonged

exposure to borderline obesity (16% higher). These effects were more pronounced for never-smokers and obesity-related cancer deaths. Being overweight in early adulthood and becoming class II obese increased cardiovascular disease mortality (2.27 times higher relative to the “stable lower-normal trajectory”).

Study 3: Effects of sustained hypothetical interventions on physical activity and TV viewing in relation to mortality in the Australian Diabetes, Obesity and Lifestyle Study (AusDiab)

The study using data from the AusDiab cohort estimated the effects of single or joint hypothetical interventions for insufficient leisure-time physical activity and prolonged TV viewing (a common leisure-time sedentary behaviour) on all-cause mortality over a 13-year period in Australian adults. The data analysis used the parametric g-formula to address some of the methodological challenges identified in the systematic review (Study 1). The findings suggested that under sustained interventions that increased weekly physical activity, mortality would have been lowered by 8% (increasing to 150-300 minutes/week if lower than 150 minutes/week) to 13% (increasing to more than 300 minutes/week for all participants), compared with having no intervention. Interventions to reduce TV viewing time, alone or in addition to a physical activity intervention, did not appear to provide additional survival benefit.

For comparison purposes, the study also included a conventional regression analysis, which used only baseline exposure and confounder data analysed using Cox regression. Although hazard ratios generated from the Cox regression model were not directly comparable to the risk ratios generated from the parametric g-formula, it appeared that the beneficial effect of physical activity might not be as evident under the conventional regression approach.

Study 4: Effects of sustained hypothetical interventions on alcohol consumption in relation to mortality in the Australian Longitudinal Study on Women's Health (ALSWH) 1946-1951 birth cohort

Using data from the ALSWH 1946-51 birth cohort, I emulated a target trial to estimate the effect of hypothetical sustained alcohol interventions initiated in midlife on 20-year all-cause mortality and 18-year cancer mortality in women. The baseline analysis using Cox regression showed lower all-cause and cancer mortality in low to moderate intake groups (up to 30g/day), and higher mortality in the >30 g/day group relative to abstention. In the per protocol analysis, a qualitatively similar relationship was observed for all-cause mortality, with highest mortality

observed in the sustained zero intake and sustained high (>30 g/day) intake intervention groups. This inverse relationship observed for low to moderate intake was less pronounced for cancer mortality in the per-protocol analysis than in the Cox regression using only baseline exposure data.

Compared with no intervention, women in the sustained light to moderate drinking intervention groups had lower all-cause mortality (17% lower for the “>10 to 20g/day” group, and 18% lower for the “>20 to 30g/day” group). In this cohort of women, no level of alcohol consumption appeared to lower cancer mortality.

8.2 Strengths and limitations of the research

Strengths and limitations of the studies included in the systematic review have been discussed in detail in Chapter 3. In this section, I will focus on consolidating strengths and limitations of the three chapters that analysed data from the MCCS, AusDiab study, and ALSWH 1946-51 birth cohort.

8.2.1 Strengths of the research

Study design and data

A key strength of the research relates to the study design and data of the three studies. The MCCS, AusDiab study, and the ALSWH 1946-1951 birth cohort are cohort studies that collected participants’ data prospectively. An advantage of the prospective design is that exposure information was collected before the development of the outcome (i.e., death), so that measurements of exposure were not biased by knowledge of death status. The three analyses, therefore, were unlikely to be affected by differential measurement error of the exposure.²⁷⁸

The relatively large sample sizes and number of deaths in the three studies provided reasonable precision of results for all-cause mortality. In the three cohort studies, vital status and date of death were ascertained through record linkage to the NDI at the Australian Institute of Health and Welfare. The Australian NDI is a national database containing death records in Australia since 1980, collected from the Registrars of Births, Deaths and Marriages in each jurisdiction, the National Coronial Information System, and the Australian Bureau of Statistics. The records are also linked with Australian National Mortality Database for cause of death information.²⁷⁹ Although some errors in linkage are expected due to incorrect personal information supplied at death registrations, and loss to follow-up would occur if participants moved overseas,²⁷⁹ a

study found that the Australian NDI showed high sensitivity (93.7%) and specificity (100%) for identifying deaths.²⁸⁰ In addition, the study found that Australian cause of death data had reasonably high sensitivity (92.5% for CVD deaths, and 95.2% for cancer deaths) and specificity (89.6% for CVD deaths, and 99.2% cancer deaths). Therefore, risk of bias due to measurement error of the outcome in the three analyses was relatively low.

The three cohort studies followed participants actively to update data on exposures. This is important because the participants likely changed their health behaviours over the long post-baseline follow-up period (up to 27 years in the three studies). Updating the information on exposures allowed studying of relationships between long-term exposure patterns and mortality outcomes. In the AusDiab study and the ALSWH 1946-1951 birth cohort, comprehensive data on confounders at all time points also allowed adjustment of time-varying confounding.

Analytic approaches

The other strength of the research relates to the use of analytic approaches that take advantage of the longitudinal data, and account for time-varying confounding when data were available.

The MCCS analysis employed a group-based trajectory approach to summarise longitudinal BMI data throughout adulthood. Notwithstanding limitations, which will be discussed later in this section, the approach respects the gradual and continuing nature of body mass development. It is particularly useful for identifying relatively homogeneous groups following similar BMI developmental courses over time, which allows comparison of disease and mortality risks of people who experienced different trajectories.²⁸¹

Most published studies estimating effects of sustained lifestyle exposures did not account for time-varying confounding affected by prior exposure level adequately, as shown in my literature review (Chapter 2) and systematic review (Chapter 3). The AusDiab and ALSWH analyses used the parametric g-formula to estimate effects of sustained exposure to physical activity, TV viewing, and alcohol consumption. With repeated measurements of exposures and confounders, using the parametric g-formula, the two analyses were able to emulate hypothetical trials of long-term lifestyle interventions while adjusting for time-varying confounding appropriately. This cannot be achieved with conventional regression. In the two analyses, sequential conditional exchangeability (described in Chapter 4) was approximated through good control for time-fixed and time-varying confounders for each time interval using the parametric g-formula. Correct model specification was validated through reproducing the

observed risk under a “no intervention” scenario. Moreover, in the absence of model misspecification, the g-formula estimates should be insensitive to the ordering of covariates.²⁷⁰ The estimates from both analyses were tested and found to be insensitive to different orders of covariates (more details provided in Chapter 6 and Chapter 7).

8.2.2 Limitations of the research

Several limitations need to be considered when interpreting the findings. I will first discuss the limitations related to the internal validity of the three studies, i.e., the validity of the estimates in the study samples. Then, I will discuss limitations pertaining to external validity related to generalisability of the effect measures from the study samples to the target populations. External validity related to transportability of the estimates to other populations is beyond the scope for this thesis and will not be discussed here.

Measurement error and misclassification of exposures

Measurement of lifestyle-related exposures is prone to errors. Firstly, the errors could arise at a conceptual level. The underlying conceptual constructs of adiposity, physical activity, sedentary behaviour, and alcohol consumption are complex. For example, excessive adiposity can be estimated using BMI (indicates total body adiposity), waist circumference (indicates central adiposity) or other anthropometric measures.¹⁷ Physical activity and sedentary behaviour can be assessed based on domains (e.g., occupational, leisure-time) and dimensions (e.g., duration, type, intensity, frequency).²⁸² Similarly, alcohol consumption comprises quantity, frequency, volume, pattern (e.g., binge drinking), and type of alcoholic beverages consumed.^{283,284} The variables used in my analyses (i.e., BMI, leisure-time active minutes, TV viewing time, and alcohol intake in grams approximated using frequency and quantity of drinking) may not represent the underlying constructs well enough to adequately assess consequent mortality.²⁷⁸ For example, excessive fat deposition, especially in the abdominal area, increases risk of a wide range of diseases hence mortality.²⁸⁵ However, BMI does not differentiate between muscle mass and body fat. Therefore, BMI may not be the best measure to demonstrate mortality differences that are due to excessive central fat deposition, which is one aspect of excessive adiposity (it is worth noting that a study showed high correlation between body mass and waist circumference [Spearman correlation=0.85] in the MCCS²¹³). Similarly, physical activity, sedentary behaviour and alcohol consumption are complex constructs that cannot be easily reported or calculated without errors.

Secondly, measurement error can be introduced by the data collection process. In the MCCA, body mass used to calculate BMI was recalled for early adulthood and self-reported at the second wave of data collection (i.e., first active follow-up). Although age- and sex-specific correction was made to the self-reported data, recalled weight was not corrected because the self-report correction formula might not be applicable to recalled weight.^{216,217} In the AusDiab study, leisure-time physical activity and TV viewing time (a common leisure-time sedentary behaviour) were assessed using the Active Australia Survey and a TV viewing time questionnaire with self-reported frequency and duration during the previous week.¹⁹⁶ Measurement error arising from the use of self-report data is well recognised, and leads to inaccurate estimates of physical activity and sedentary behaviour, and usually attenuation of their effects on mortality.^{106,183,184} Alcohol consumption in ALSWH was also assessed using questionnaires, which are known to systematically underestimate true alcohol intake.²⁸⁶ Also, at most waves, the questionnaire only asked about the participants' frequency and quantity of alcoholic beverages consumption. No data on type of alcoholic beverages consumed were collected, therefore, daily pure ethanol intakes could only be approximated.

Finally, misclassification may arise when grouping continuous variables into categories, for example, when I classified physical activity (minutes/week) and alcohol consumption (grams/day) into guideline-based categories. Although the participants' vital status (or researchers' knowledge of their vital status) was unlikely to have affected the misclassification, a study suggested that categorisation of continuous variables may change measurement error from non-differential to differential.²⁸⁷

Residual confounding

In AusDiab and ALSWH, confounder data were collected repeatedly over time. Therefore, I was able to adjust for time-fixed confounding and time-varying confounding for each time interval using the parametric g-formula. However, in the MCCA analysis, application of the parametric g-formula was not possible because of the lack of time-varying confounder data to approximate sequential conditional exchangeability. The estimated BMI trajectories were constructed from early to late adulthood. Only body mass (for BMI calculation) was recalled for early adulthood. Information on potential confounders for that life period was not collected. Also, only data for some confounders were recorded at the second wave of data collection. Therefore, inadequate adjustment for early adulthood confounders that influenced both BMI trajectories and mortality is a concern. However, I was able to control for sociodemographic factors measured in mid-adulthood (at the time of entry to the MCCA) that had not changed

(including birth cohort, sex, country of birth) or were relatively stable since early adulthood (including height, area-based socioeconomic status, and level of education) and baseline values of lifestyle-related confounders. However, it is worth noting that the MCCS analysis is subject to the inherent dilemma of conventional regression methods when there is time-varying confounding (described in detail in Chapter 4), which is having to choose between over-adjustment and under-adjustment of confounding.¹⁸⁷ For instance, I controlled for baseline (midlife) physical activity in the analysis, but it could be on the causal pathway from early adulthood BMI to mortality. Adjusting for it would have blocked part of the effect of early adulthood BMI, but not adjusting for it would result in uncontrolled confounding for the effect of BMI later in life on mortality.

Despite controlling for measured confounders, and the application of appropriate statistical methods whenever possible, residual confounding may have occurred in the three analyses. Firstly, most data on confounders were self-reported. Measurement error or misclassification of these variables may have weakened the ability to control confounding. For example, the ALSWH questionnaire response for non-drinking at baseline did not distinguish between lifetime abstainers and former drinkers. Although I adjusted for past alcohol consumption in late teens, twenties, and thirties, the weekly intake levels were recalled and in broad categories (i.e., no alcohol, 1-7 drinks, 8-14 drinks, and 15 or more drinks) and were likely insufficient to control for confounding from past alcohol intake. Secondly, the time interval lengths between data collection waves may have contributed to residual time-varying confounding. The intervals were approximately four to nine years in the MCCS, five to seven years in the AusDiab study, and two to three years in the ALSWH 1946-1951 birth cohort. A simulation study found that bias in the estimation of effects increased with measurement interval length.²⁷³ The study also found that when confounding is strong, the true effect of the exposure could not be fully recovered under a yearly interval-measurement scenario even when g-methods were used. However, the study showed that results were less biased compared with ignoring time-varying confounding completely.²⁷³

Finally, the questionnaires in the three cohort studies did not ask about intentions or reasons for exposure changes, which is critical information for confounding control. As an example, studies have reported that moderate alcohol consumption is associated with lower mortality than alcohol abstention.^{73,265} This is sometimes interpreted as demonstrating moderate alcohol consumption is beneficial for reducing mortality. However, some studies showed that people who were diagnosed with serious illness or feeling unwell in general tended to cease alcohol

consumption.⁷⁷ The observed lower risk in moderate drinkers compared with non-drinkers could be simply due to the fact that people in poor health (hence more likely to die) stopped drinking. Similarly, underlying diseases often cause unintentional weight loss or lack of physical activity, and lead to higher risk of death. Inadequate control of this form of confounding (sometimes referred to as reverse causation) would bias the estimate and make a supposedly healthy lifestyle behaviour appear harmful for mortality. Although the three analyses each controlled for a reasonable range of comorbidities and/or self-perceived general health, these variables may not have fully blocked confounding by deteriorating health.

Selection of participants into the analysis

Selection of participants into the analysis may have introduced bias when the selection was affected by both the exposure and the outcome (death), or by both the exposure and a cause of the outcome.²⁸⁸

Selection bias was particularly a concern in the MCCS analysis, which included participants who had at least three BMI data points. The aim was to allow modelling of quadratic trajectories over time. This restricted the sample to participants who had survived to the third wave of data collection, and earlier BMI may have affected that survival (sometimes referred to as survival bias). Therefore, the selection was affected by both the exposure and the outcome.

In addition, longitudinal studies are prone to missing data that can lead to selection bias too. In all three cohorts, there were missing data because of non-attendance at one or more active follow-ups, or missing response to questionnaire items among the attendees. Non-attendance may be related to poor health, as people who were ill (hence more likely to die) were more likely to miss out on active follow-ups. Also, participants who missed out on follow-up waves were likely to have different exposure levels than those who attended. In the AusDiab and ALSWH studies, I used multiple imputation by chained equations to impute the missing data, therefore, all participants eligible at baseline were included in the analyses.^{253,289} The MCCS analysis was, however, restricted to participants with complete exposure and confounder data for at least three time points. Participants included in the analysis not only had to be alive at the third data point, but they may also have been in better health hence less likely to die than participants excluded. In fact, the excluded participants were mainly those who had the first two data points (i.e., BMI measured at baseline and recalled for age 18-21). They had higher mean BMI for the first two time points and higher odds of death at the end of the study compared with those selected into the analysis. In this case, bias arose because selection of

participants into the analysis was affected by both BMI and health status (a cause of death). Excluding them may have led to underestimation of mortality in the overweight or obese trajectories. Future research that integrates quantitative bias analysis would help gain insights to the magnitude of such underestimation.

Limitations of the statistical analysis methods

Chapter 3 (discussion, sources of bias in existing studies) and Chapter 4 (section 4.3.2, estimating the effect of time-varying exposure) have detailed the biases that may arise from using regression models in the presence of time-varying confounding. The limitations when regression was applied in the MCCS analysis have been elaborated on in sections 8.3.2 and 8.3.3.

Although the parametric g-formula allows estimation of long-term exposure effects without introducing biases due to conditioning on a common effect or a mediator as a regression model would, the identification assumptions (i.e., sequential conditional exchangeability, positivity, and consistency, as described in Chapter 4) and estimation assumptions (i.e., no measurement errors and no model misspecification) need to be considered when interpreting the results. Confounding by unmeasured or mismeasured confounders would have affected sequential conditional exchangeability; an ill-defined exposure or intervention could have affected consistency. Positivity is less of concern because the parametric g-formula is an outcome-regression-based method, which can be used when positivity does not hold perfectly, assuming the outcome model can extrapolate beyond the data.²⁰² Moreover, measurement errors are inevitable in measuring lifestyle-related exposures, and some degree of model misspecification is unavoidable in the parametric g-formula. These assumptions are not expected to hold perfectly given the limitations discussed in earlier sections (sections 8.3.1 to 8.3.3).

It is also worth noting that, in theory, the parametric g-formula is subject to the “g-null paradox”, which means the null hypothesis (for instance, the hypothetical alcohol interventions emulated in ALSWH study have no effect on mortality), even if true, will be rejected in a large enough sample because the estimated value of the g-formula for the outcome generally depends on the exposure history.^{202,256} For this reason, the use of the parametric g-formula has not been popular in the literature until more recently when the problem was revisited and it was suggested that the “g-null paradox” likely has a small impact on estimates in practice.^{202,278}

The limitations discussed so far (related to measurement of the exposure, confounding, selection of participants, and statistical methods) mainly concerned internal validity. In

summary, the risk of bias affecting the interval validity of my results is summarised in Table 8-2, using the preliminary ROBINS-E tool¹¹⁴ which was also used to assess potential biases in studies included in my systematic review chapter.

Table 8-2 Summary of risk of bias for each study in this thesis, according to the preliminary ROBINS-E (Risk Of Bias In Non-randomised Studies - of Exposures) tool

Risk of bias due to	Study		
	MCCS ^a	AusDiab ^b	ALSWH ^c
Confounding	Moderate	Low	Serious
Selection of participants	Serious	Low	Low
Classification of exposure	Low	Moderate	Moderate
Departures from measured exposure	Low	Low	Low
Missing data	Moderate	Low	Low
Outcome measurement	Low	Low	Low
Selection of the reported results	Low	Low	Low

Note that “Low” does not indicate being completely free from bias, but a generally low risk of it. All three studies had low risk of bias due to departures from measured exposure (time-varying nature of the exposures were accounted for in the statistical approaches), outcome measurement error (ascertained through National record linkage) and selective reporting of results (reported effect estimates were not selected on the basis of the results).

^a The major risk of bias in the MCCS analysis came from the selection of participants into the analysis, which was based on survival to at least the third BMI assessment. Other sources of bias included insufficient adjustment for time-varying confounding, and not accounting for missing data.

^b The main risk of bias in the AusDiab analysis arose from measurement and classification of the exposure through self-reported questionnaire of leisure-time physical activity.

^c The main risk of bias in the ALSWH analysis arose from approximation of daily alcohol intake (g/day) using self-reported frequency and quantity of alcohol consumption without information on type of alcoholic beverages consumed, potentially inadequate information to control for the confounding by reasons of quitting or reducing alcohol consumption, and inadequate information to control for past alcohol intake levels (e.g., lifetime abstainers versus former drinkers)

Generalisability of findings to the target populations

Generalisability refers to the extent to which the effect measures obtained from the study samples are unbiased when used to make inference back to the full target populations.²⁹⁰ Even if the effect estimates of my studies had good internal validity, several limitations may affect the generalisability to the target populations: adults of the metropolitan Melbourne population (the MCCS analysis), adults in the general population of Australia (the AusDiab analysis), and middle-aged women in Australia (the ALSWH analysis).

It is possible that participants who consented to participate in the three cohort studies had different characteristics from those who were sampled but declined to participate. In the AusDiab study, higher percentages of participants had completed high school, technical education or University than non-respondents to the study.¹⁹¹ Women in the ALSWH 1946-51 birth cohort were more likely to have University education and Australian-born than the

Australian census of women of the same age at the time of recruitment.¹⁹² The recruitment strategies may also have led to different distributions of participant characteristics in the study populations than in the target population. As a result of a deliberate oversampling strategy, the MCCS cohort has higher proportions of participants of older age groups, and Italian and Greek born participants than the metropolitan Melbourne population aged between 40 and 70 years at the time of recruitment.¹⁹⁰ At recruitment of the AusDiab study, census collection districts classified as rural, containing fewer than 100 eligible adults, or containing more than 10% indigenous population were excluded.¹⁹¹ Similarly, researchers who established the ALSWH study acknowledged that, despite efforts, minority groups were under-sampled. These included indigenous women, women with disability, institutionalised women, and women from non-English speaking background.¹⁹³ As a result of the non-representativeness, it is possible that the distribution of potential effect modifiers differed between the study samples and the target populations. This would affect the generalisability of the findings directly to a target population without re-weighting to the prevalence of effect modifiers in the target population.²⁷⁸

In longitudinal studies that last for decades, even effect measures with good generalisability to the target population at the time of recruitment may not have the same generalisability at later times when results are drawn to inform public health decisions. For instance, in the MCCS analysis, most participants started with normal BMI at age 18-21 years, which is no longer the case for Australian adults nowadays. About 15% of young adults (age 18-21 years) born between 1994 and 1997 in Australia were obese. This figure is almost doubled compared to that of their counterparts born 20 years earlier (8%) and is much higher than in our sample born before 1950 (2%). The set of BMI trajectories identified in the MCCS therefore likely does not reflect the mixture of trajectories Australian adults are following nowadays. It is also worth noting that TV viewing, once the most common leisure-time sedentary behaviour, may not be as relevant as it was during the AusDiab times because of the expansion of technologies for other forms of sedentary entertainment. Therefore, when generalising the findings about TV viewing's effect to the target population nowadays, one should consider the current circumstance that low TV viewing time may be accompanied by hours of other types of sedentary entertainment in some individuals. In addition, it is possible that the prevalence of effect modifiers has changed over time, which could affect the generalisability of the estimates to the target populations nowadays. Furthermore, overall mortality has decreased in the last few decades in Australia.²⁹¹ This could affect the absolute and relative mortality comparisons as the mortality under the "status quo" has changed.

In the AusDiab and ALSWH analyses, I estimated average causal effects of hypothetical population interventions. Even if these estimates have perfect internal validity, they are not readily generalisable to target populations with different distributions of exposure. In my AusDiab analysis, close to 60% of participants were classified as sufficiently active (i.e., at least 150 mins/week). Results from the Australian National Health Surveys, however, showed that the percentage of Australian adults with sufficient physical activity was consistently low from 1989 to 2011 (about 40%)²⁵⁹ and recently increased to 45% in 2017-18.²⁹² Considering that, the hypothetical physical activity interventions considered in my study may have a greater benefit in the general population than in my sample. On the other hand, in my ALSWH analysis, about 14-15% women consumed more than two standard drinks per day, which was higher than the 10% in Australian women of similar age range in 2017-18.²⁷⁷ Therefore, the population effects of the alcohol-reducing interventions I estimated may be even smaller for women in this age range in the general population.

In summary, the findings in this thesis may not be readily generalisable (in terms of quantitative generalisability) to the target populations at the time when study population were drawn (i.e., in the 1990s), or at the time when findings are to be used to inform public health decisions (in the future). There are quantitative generalisability methods available to formally generalise causal effects from a study sample to a well-defined target population.^{290,293} However, the topic of quantitative generalisability is beyond the scope of this thesis, therefore, will not be discussed further.

Small number of cases for cause-specific mortality outcomes

In my analyses of cause-specific mortality, the precision of the estimates was relatively low because of the small number of cause-specific deaths in some exposure categories. Some effects on cause-specific mortality outcomes were not examined due to small numbers of deaths (Table 8-1), including effects of sustained physical activity and TV viewing on cardiovascular disease and cancer mortality in the AusDiab analysis, and the effect of midlife alcohol consumption on cardiovascular disease mortality in the ALSWH analysis. These effects have been investigated extensively in studies with single-timepoint exposures,^{71,106,294,295} and are worth examination using longitudinal data to further understand the effects of long-term exposure or intervention.

8.3 Implications and directions for future research

The aim of the thesis was to examine the impact of adulthood lifestyle-related exposures on mortality using exposure data from multiple time points in existing cohort studies. The thesis has demonstrated that, to study such exposures, it is important to use analytic approaches leveraging the longitudinal exposure and confounder data. In this section, I will discuss what my findings add to existing knowledge on this topic, their implications, and directions for future research.

8.3.1 Contribution to existing knowledge and public health implications

As summarised in Table 8-3, the current classification of BMI and guidelines for physical activity, sedentary behaviour, and alcohol consumption rely predominantly on studies of disease risk and mortality using exposures measured at one time point. Findings of this thesis contribute towards the accumulating body of evidence on mortality effects of lifestyle-related factors measured multiple times over adulthood, thus help refining public health guidelines.

The MCCS analysis identified BMI trajectories across adulthood, which included a specific group following a prolonged borderline obesity trajectory that had elevated mortality risk that was comparable to more obese trajectories. The results also showed that midlife obesity increased mortality even if BMI was normal at a younger age. These findings imply that public health promotion is needed to emphasise the importance of ongoing weight maintenance in adults having normal BMI. The study did not find any weight loss trajectories during adulthood because most participants started with a normal BMI. However, given the increasing prevalence of overweight and obesity in Australia, particularly in young adults, there may be a higher disease burden and mortality from potentially more high-risk trajectories (e.g., consistently obese) that did not emerge in the MCCS population born before 1950. This points to the pressing need for research efforts to identify critical periods for obesity prevention, and to look for effective population interventions to encourage weight reduction and mitigate the detrimental health effects of elevated BMI for the increasing number of people entering adulthood being already overweight or obese. This again illustrates the importance of not relying on measurement at a single point in time when studying BMI (or other measures of adiposity) over adulthood and subsequent health and mortality.

The AusDiab analysis is the first study that employed a counterfactual framework of causal inference to simulate potential mortality outcomes under hypothetical population interventions on physical activity, TV viewing, or them jointly. As shown in my systematic review, while

several existing studies of long-term physical activity accounted for time-varying confounding with appropriate statistical methods, no published mortality study using longitudinal sedentary behaviour data has accounted for time-varying confounding. Therefore, my study contributed to fill this research gap. My findings suggested that results from a typical analytic approach using baseline exposure may lead to undervaluing the survival benefits of physical activity, compared with results using physical activity measured at multiple time points. Furthermore, my findings suggested that interventions in adulthood to increase physical activity appear beneficial for lowering mortality, and interventions to reduce TV viewing time may not have such beneficial effect. This would provide new insights into potential gain from physical activity interventions, and may stimulate additional public health expenditure into physical activity promotion.

The ALSWH analysis contributed to the scarce literature on the topic of women's alcohol consumption and mortality that used exposure data from multiple time points.⁸⁰ I estimated counterfactual outcomes under hypothetical interventions of midlife alcohol consumption. One of the interventions I simulated corresponds to the previous Australian guidelines to reduce health risks from alcohol consumption, which recommended less than two standard drinks per day (containing less than 20g of pure ethanol) by adults to reduce alcohol-related harm over a lifetime.²⁹⁶ The findings suggested that an intervention to reduce alcohol consumption to no more than two standard drinks per day may result in only slightly lower all-cause mortality than no intervention. The small reduction in both risk difference and risk ratio relative to "status quo" implied that, in a population of generally light-drinking women, interventions to reduce alcohol consumption may have limited benefit for reducing mortality. It is worth noting that the guidelines have been revised recently to recommending no more than ten standard drinks per week for healthy adults to lower risk of alcohol-related disease or injury.⁷⁸ The revision was made after the ALSWH analysis was completed. I needed to be physically located at the University of Queensland for data analysis. Because of COVID-19 travel restrictions, I was unable to update the analysis according to the new guidelines.

Table 8-3. Current classifications of BMI, and international and Australian guidelines for physical activity, sedentary behaviour, and alcohol consumption for adults, and evidence referred to about mortality.

Classification, Guideline, or recommendation for adults		Evidence referred to about mortality
BMI	International: WHO classifications of BMI¹⁹: Underweight – Below 18.5 kg/m²; Normal – 18.5 to 24.9 kg/m²; Overweight – 25.0 to 29.9 kg/m²; Class I obesity – 30.0 to 34.9 kg/m²; Class II obesity – 35.0 to 39.9 kg/m²; and Class II obesity – 40 kg/m² or greater. Some Asian countries adopted lower cut-off values for overweight and obesity because of higher percentage of body fat in general and higher proportion of disease risk factors than Western populations at the cut-off of 25 kg/m².²⁹⁷ Australian: The international WHO classifications are widely used in western populations including Australia.	No specific reference was made to evidence about mortality. The cut-off values for overweight and obesity were based on relationship between BMI and risk of comorbidities, which were largely based on observational studies using single BMI measurement.¹⁹
Physical activity and sedentary behaviour	International: WHO 2020 guidelines on physical activity and sedentary behaviour²⁹⁸ - At least 150 to 300 minutes of moderate intensity aerobic physical activity, or at least 75 to 150 minutes of vigorous intensity aerobic physical activity, or an equivalent combination throughout the week. - At least 2 days per week engagement in muscle-strengthening activities at moderate or greater intensity. - Limit sedentary time and replace with physical activity of any intensity. - Do more than recommended levels of physical activity to reduce detrimental effects of high sedentary time. Australian: Australia's physical activity and sedentary behaviour guidelines¹⁰⁹ - Same recommendations for physical activity as in the WHO guidelines. - Minimise prolonged sitting. - Break up long periods of sitting.	International: Evidence was drawn about all-cause mortality from studies based on physical activity and sedentary behaviour measured at one time point.^{13,299} Australian: Evidence was drawn from studies using single-timepoint exposure for all-cause and cardiovascular disease mortality.²⁴⁸
Alcohol	International: Currently, there is no international guideline on low-risk drinking. Australian: Australian guidelines to reduce health risks from drinking alcohol.⁷⁸ - To reduce the risk of harm from alcohol-related disease or injury in healthy adults, drink no more than 10 standard drinks (containing no more than 100 grams of pure ethanol) a week, and no more than 4 standard drinks (containing no more than 40 grams of pure ethanol) on any single day. - The less you drink, the lower your risk of harm from alcohol.	Australian: One meta-analysis was considered when drawing evidence about long-term mortality risk of alcohol consumption, in which the primary exposure of interest was mean daily alcohol consumption assessed at baseline.¹⁵

BMI-body mass index; WHO-World Health Organization.

8.3.2 Causal inference from observational data

Another important implication of my research is its contribution towards the growing evidence base demonstrating explicit causal inference from observational studies. The overarching aim of studying mortality effects of lifestyle-related exposures in this thesis was motivated by the goal of identifying opportunities to improve population health through intervening on these modifiable factors. Randomised controlled trials are often not feasible (e.g., infeasible to randomise adults to receive 10-year physical activity interventions) or unethical (e.g., unethical to randomise women to drink harmful amounts of alcoholic beverages for 10 years). Without randomised controlled trials, the effects of exposure to or intervention on these factors can only be inferred from observational data. Although results from observational studies are often referred to as associations rather than causal effects, the way the ‘associational’ estimates have been used to guide public health decisions (e.g., through interventions, guidelines, or policy changes) suggests that they have been used with causal interpretations. For example, the physical activity guidelines imply that 150 to 300 minutes of moderate to vigorous physical activity every week would lead to health benefits in adults compared with not exercising.

The analyses in this thesis were planned with the goal of taking a step away from examining associations to answering causal questions. This included formulating well-defined causal questions, constructing directed acyclic graphs to guide confounder selection, and making causal assumptions explicit. Assumptions underlying valid causal inference from observational data are often considered as strong assumptions (e.g., no unmeasured confounding, no measurement error, no model misspecification). Therefore, it is important to openly discuss potential violation of these assumptions, to allow assessment of how seriously one should consider the estimates to have a causal interpretation.²⁰² I acknowledge that each analysis in this thesis was subject to its own limitations, and the analysis of the MCCS study in particular could be improved in terms of formalising the causal inference attempt. Potential biases that would lead to deviations from these causal assumptions in each study have been explicitly discussed in this chapter (section 8.2.2, limitations of the research).

The AusDiab and ALSWH studies estimated the effects of population interventions, which are more policy-relevant than exposure effects traditionally reported in many studies. Exposure effects, i.e., the mortality contrast between the exposed and the unexposed, may provide more understanding about the aetiological effect of the exposure than the estimated effect of a public health intervention in a given population.²⁴⁴ For example, an exposure effect comparing mortality had everyone exercised for 150 minutes weekly to everyone doing no exercise does

not answer the question of how mortality would have changed in a population under a certain intervention compared with “status quo”. In contrast, the population intervention effects estimated in the AusDiab and ALSWH studies are the estimated causal effects of possible population interventions applied to specific populations with a given distribution of the exposure to be intervened against. Mortality under such hypothetical interventions was compared with mortality under the “status quo” scenario, which made a more realistic and policy-relevant comparator than “had no one done any exercise at all”.

8.3.3 Future research

Future research is needed to accumulate more evidence on the mortality impacts of lifestyle-related exposures measured multiple times across adulthood. In the absence of feasible randomised controlled trials, making inference through observational studies, especially cohort studies, remains one of the main approaches to answer questions about health and survival benefits of long-term lifestyle-related exposures or interventions. As discussed previously, there is a need to formalise causal inference from observational data if the goal of the research is causal.³⁰⁰⁻³⁰² Additionally, a healthy scepticism and discussion around causal assumptions and potential deviations is a necessary step towards a more formal causal inference from observational data.²⁰²

The directed acyclic graph (DAG) is an increasingly popular tool in causal inference for declaring assumptions about underlying mechanisms connecting exposure and outcome, and identifying variables for confounding control.^{205,303} With the increasing availability of longitudinal lifestyle exposure data, DAGs are particularly helpful in visualising the time-varying nature of these exposures, and highlighting potential biases that may arise from complex time-varying confounding, as demonstrated in this thesis. Despite the advantages DAGs offer, a recent review suggested that clarity of application and reporting of DAGs in applied health research could be improved in the future.³⁰⁴

Apart from the parametric g-formula used in this thesis, other g-methods such as inverse probability treatment weighting (IPTW) of marginal structural models (MSM) and g-estimation of structural nested models are available to deal with analytic challenges arising from complex longitudinal data.^{187,305} Additionally, future studies could make use of the recent development in integrating machine learning techniques with doubly robust estimators (as opposed to singly robust estimators from outcome regression in g-formula, or propensity score in IPTW of MSM) for more advantageous statistical properties.^{306,307} For example, the use of

targeted maximum likelihood estimation with non-parametric machine learning techniques helps protect against bias arising from parametric model misspecification, while offering double robustness (i.e., the method will yield unbiased estimates if either the exposure or the outcome mechanism is consistently estimated).^{306,308}

From a longitudinal perspective, it is important to understand why people followed a certain trajectory of behaviour over time. To control for confounding adequately, it is important to know whether the reasons for any lifestyle changes were in fact the causes of the health outcomes of interest. For example, whether major illnesses were the actual reason for both weight loss and increased mortality. However, collection of such behavioural information is often lacking and needs to be actively integrated at study design stage to reduce confounding.

Given the growing evidence on the health impact of lifestyle-related exposures before adulthood, ideally, future research would benefit from having exposure and confounder data from early life.^{309,310} It would help improve the understanding around the long causal chains starting early in life and offer a holistic view on the role of lifestyle exposures from a life course perspective. Such future research would also help guide early interventions to mitigate long-term adverse health outcomes including mortality.

In studies without early-life data, there is a need to explicitly define research questions so that they can be answered with the data available. For example, instead of vaguely asking if alcohol consumption impacts mortality, one could ask whether modifying alcohol consumption in midlife would change mortality compared with not modifying it. This brings out the importance of an analysis plan. The target trial emulation approach used in my ALSWH analysis is a powerful tool for defining a research question explicitly at analysis planning stage. It assists in clarifying what is to be estimated (i.e., target trial specification) and mapping the ideal study to an actual study (i.e., emulation using observational data).²⁶⁷

As mentioned in section 8.2.2 (limitations of the research), imperfect measurement of variables, confounding, and selection of participants are likely to introduce bias in the analysis. Even with application of appropriate statistical methods, these limitations are unavoidable with observational data. A recent systematic review showed that quantitative bias analysis (sometimes referred to as sensitivity analysis) is rarely used in epidemiological research, but the applications have been increasing over time.³¹¹ Future studies could incorporate quantitative bias analysis to evaluate the impact of potential biases on the direction, magnitude, and uncertainty of the estimates.³¹²⁻³¹⁴

Finally, a single form or source of evidence is likely insufficient to draw definitive conclusions about causal effects of an exposure or an intervention. Future research should accumulate and synthesise evidence generated using different causal inference approaches (also known as triangulation of evidence). Triangulation addresses a causal question by integrating results from approaches that are subject to different and unrelated forms of bias.³⁰ To facilitate triangulation of evidence, future studies would need to explicitly acknowledge their assumptions and key sources of bias.³⁰ Furthermore, in addition to asking what the mortality effect of an exposure or intervention is, future research could also explore why it has such an effect. Randomised controlled trials examining effects of health interventions on biomarkers and intermediate health outcomes, and causal mediation analysis are needed to understand the mechanisms that cause mortality.^{315,316}

8.4 Conclusion

Although a large body of epidemiological evidence has accumulated on lifestyle-related exposures and mortality, many studies contributing to this were based on exposure data measured at a single time point, or were subject to limitations due to methodological challenges arising from analysing longitudinal data as found in the systematic review. This thesis used existing cohort studies that have collected multiple waves of data and adopted increasingly accessible statistical methods for longitudinal data analysis to revisit mortality effects of lifestyle-related factors, respecting their time-varying nature. Studies in this thesis examined the mortality effects of adulthood BMI trajectories, hypothetical sustained interventions on physical activity, TV viewing, and midlife alcohol consumption. The studies showed that, with data assessed at multiple time points, one could estimate mortality effects of exposure patterns over time, which cannot be achieved using single-time-point measurements. The studies also demonstrated the use of observational data to emulate a target trial that is infeasible or unethical in a real-world setting. When analysed with appropriate statistical methods, exposure and confounder data assessed at multiple time points can be used to estimate potential mortality outcomes under hypothetical long-term lifestyle interventions.

The findings of this thesis demonstrated that midlife obesity increases mortality even when BMI was normal in early adulthood, and prolonged exposure to borderline obesity could increase mortality, compared with maintaining a higher-normal BMI. This indicates the importance of weight maintenance throughout adulthood. The findings also show that sustained

interventions during adulthood to increase leisure-time physical activity could lower all-cause mortality, and that there might be limited gain from intervening on TV viewing time in a relatively healthy population, alone or in addition to physical activity interventions. Finally, the findings suggest that, compared with having no alcohol intervention for women in their midlife, intervention of moderate alcohol consumption may lower all-cause mortality but not cancer mortality, while high intake intervention (i.e., consuming more than three standard drinks per day) would increase both all-cause and cancer mortality over the long term. These findings should be interpreted in light of limitations of the research.

Collectively, the research presented in this thesis emphasises that, to study time-varying lifestyle-related exposures, it is important to not rely on a one-off measurement and to use analytic approaches that could integrate multiple data points available in existing cohort studies. The group-based trajectory approach contributes to the understanding of mortality outcomes experienced by individuals who followed different BMI developmental course over adulthood. The two applications of the parametric g-formula demonstrated estimation of causal effects of sustained population interventions, producing policy-relevant evidence for real-world impact.

Future research should leverage data from existing longitudinal cohorts, while addressing the main methodological challenges. This would help provide a greater insight into mortality effects of initiating or maintaining a certain health behaviour, guide population interventions, and refine evidence for guidelines and recommendations.

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Appendices

Appendix A: Supplementary material related to Chapter 3

This section presents supplementary material related to the following publication:

Yi Yang, Suzanne C Dixon-Suen, Pierre-Antoine Dugué, Allison M Hodge, Brigid M Lynch, Dallas R English. Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings. *International Journal of Epidemiology* 2021; dyab181, doi:10.1093/ije/dyab181

Supplementary material

Supplementary Figure 3-1. A simplified causal diagram used to guide risk of bias assessment for confounding

Supplementary Figure 3-2. Causal diagram: time-varying confounding affected by prior physical activity or sedentary behaviour

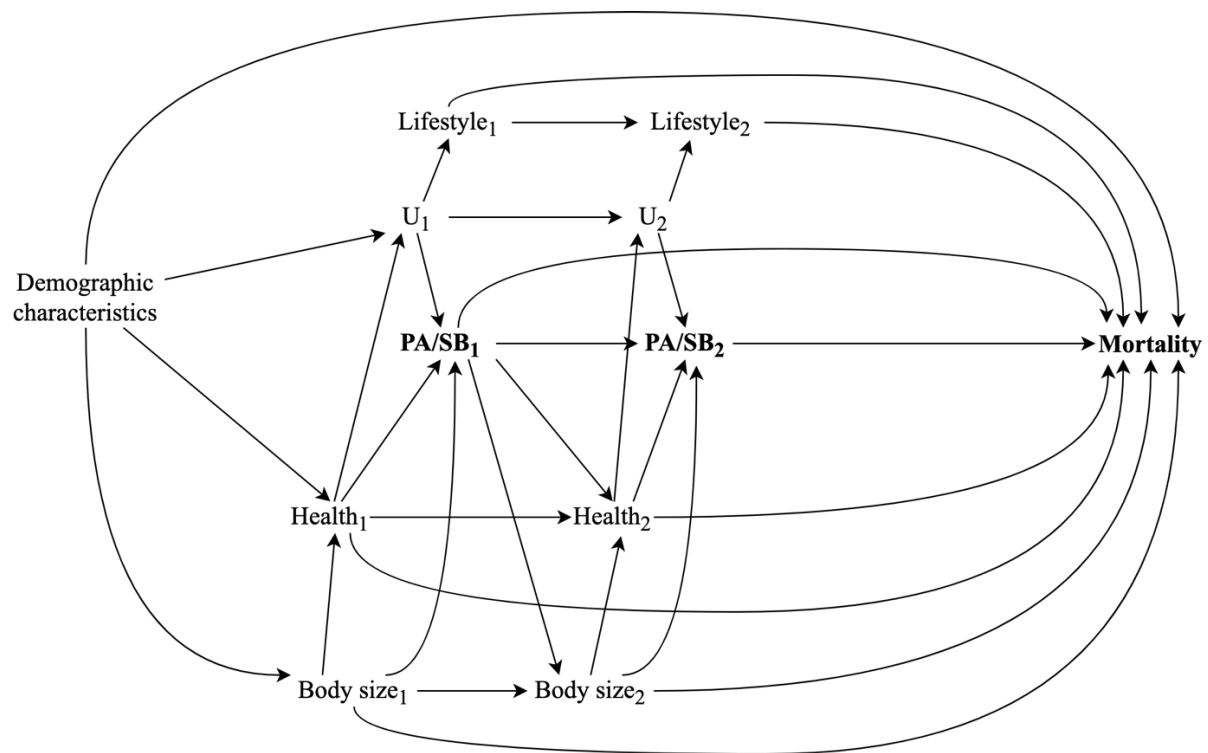
Supplementary Figure 3-3. Causal diagram: participant selection affected by prior physical activity or sedentary behaviour and vital status.

Supplementary Table 3-1. Search terms for database searching

Supplementary Table 3-2. List of excluded studies by primary reason for exclusion

Supplementary Table 3-3. Relative risks and 95% CIs between physical activity (time-varying exposure or averaged exposure) and all-cause, CVD and cancer mortality

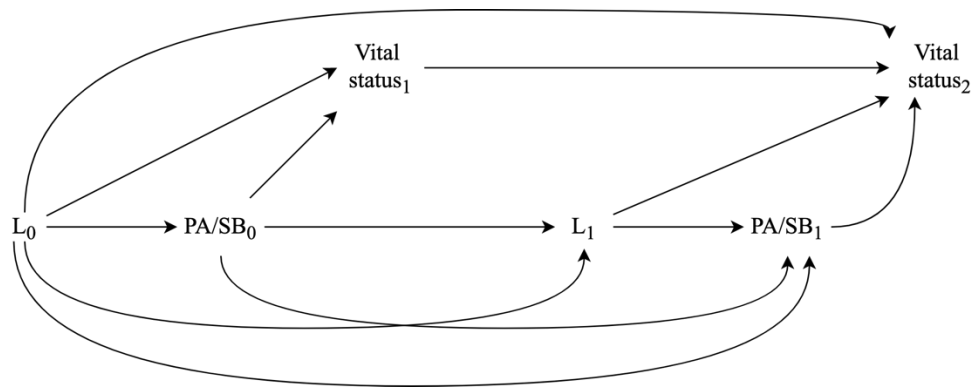
Supplementary Figure 3-1. A simplified causal diagram used to guide risk of bias assessment for confounding



Arrows from demographic characteristics to time 2 variables, and from time 1 confounders to time 2 variables were left out to make the diagram more readable without affecting the argument.

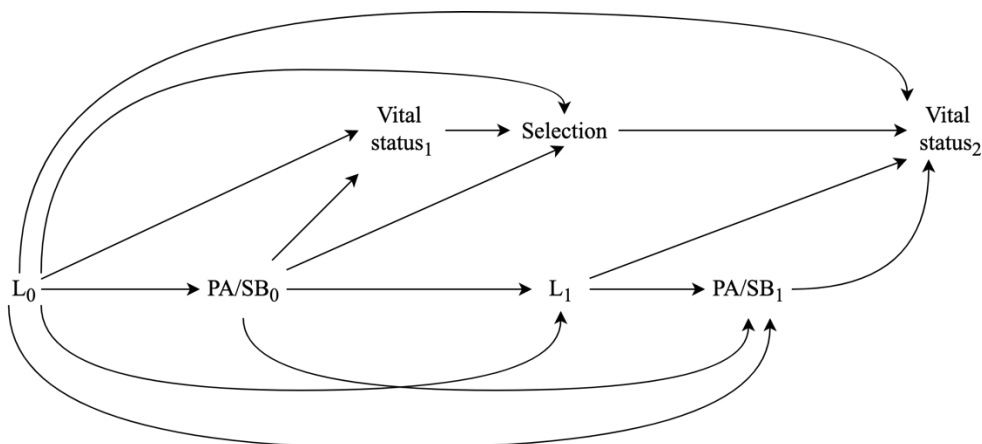
PA: physical activity; **SB:** sedentary behaviour; **U:** Unmeasured factors (e.g. health consciousness) that affects one's lifestyle-related habits, the assumption was that an individual's lifestyle habits co-existed because of U, and U were captured by one's lifestyle choices (i.e., no direct arrow from U to mortality); **Demographic characteristics:** Sex, age, socioeconomic status, education, country of birth; **Health:** Health-related factors or comorbidities that affect PA/SB and mortality; **Lifestyle:** Other lifestyle factors such as smoking, diet, and alcohol. **Body size:** body size measures such as body mass index, or waist circumference.

Supplementary Figure 3-2. Causal diagram: time-varying confounding affected by prior physical activity or sedentary behaviour



PA: physical activity; SB: sedentary behaviour; L: confounders affected by prior exposure; subscript indicates time point.

Supplementary Figure 3-3. Causal diagram: participant selection affected by prior physical activity or sedentary behaviour and vital status.



PA: physical activity; SB: sedentary behaviour; L: confounders affected by prior exposure; selection: participant selection into the analysis; subscript indicates time point.

Supplementary Table 3-1. Search terms for database searching

Database: Embase Classic+Embase 1 (mortality or death).ti,ab,kw. 2 ((Physical activity or physical inactivity or walk* or sport* or exercise* or sedentary behav* or sit or sitting or TV or television or screen time or cycling or tennis playing or playing tennis or running or jogging) adj3 (history or chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent)).ti,ab,kw. 3 (Exercise/ or Sedentary Behavior/) and (chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent).ti,ab,kw. 4 2 or 3 5 1 and 4 6 limit 5 to (human and (article or article in press))
Database: Ovid Emcare 1 (mortality or death).ti,ab,kw. 2 ((Physical activity or physical inactivity or walk* or sport* or exercise* or sedentary behav* or sit or sitting or TV or television or screen time or cycling or tennis playing or playing tennis or running or jogging) adj3 (history or chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent)).ti,ab,kw. 3 (Exercise/ or Sedentary Behavior/) and (chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent).ti,ab,kw. 4 2 or 3 5 1 and 4 6 limit 5 to human
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1 (mortality or death).ti,ab,kw. 2 ((Physical activity or physical inactivity or walk* or sport* or exercise* or sedentary behav* or sit or sitting or TV or television or screen time or cycling or tennis playing or playing tennis or running or jogging) adj3 (history or chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent)).ti,ab,kw. 3 (Exercise/ or Sedentary Behavior/) and (chang* or over time or lifetime or sustain* or prolong* or chronic or trajector* or intervention* or pattern* or modification* or time varying or time-varying or time dependent or time-dependent).ti,ab,kw. 4 2 or 3 5 1 and 4 6 limit 5 to humans
Database: Scopus (TITLE-ABS (mortality OR death)) AND (TITLE-ABS ("Physical activity" OR "physical inactivity" OR walk* OR sport* OR exercise* OR "sedentary behav*" OR sit OR sitting OR tv OR television OR "screen time") W/3 TITLE-ABS (chang* OR "over time" OR lifetime OR sustain* OR prolong* OR chronic OR traject* OR intervention* OR pattern* OR modification* OR "time varying" OR time-varying OR "time dependent" OR time-dependent)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")))
Database: Web of Science (ti=(mortality or death) or ab=(mortality or death)) AND (ti=("Physical activity" or "physical inactivity" or walk* or sport* or exercise* or "sedentary behav*" or sit or sitting or TV or television or "screen time") or ab=("Physical activity" or "physical inactivity" or walk* or sport* or exercise* or "sedentary behav*" or sit or sitting or TV or television or "screen time")) AND (ti=(chang* or "over time" or lifetime or sustain* or prolong* or chronic or traject* or intervention* or pattern* or modification* or "time varying" or time-varying or time dependent or time-dependent) or ab=(chang* or "over time" or lifetime or sustain* or prolong* or chronic or traject* or intervention* or pattern* or modification* or "time varying" or time-varying or time dependent or time-dependent)) AND DOCUMENT TYPES: (Article)

Supplementary Table 3-2 List of excluded studies by primary reason for exclusion

Primary reason ^a for exclusion	N	Studies
Exposure of interest was not physical activity or sedentary behaviour	29	1-29
Outcome of interest was not mortality	44	30-73
Background article or review	58	74-131
Exposure data were available for <2 time points	132	132-263
Study conducted within subpopulation with pre-existing disease	52	264-315
No individual level data	5	316-320
Methodology paper	1	321
No full text available	2	322, 323
Superseded by more recent study	2	324, 325

^a Some studies are ineligible for inclusion for multiple reasons. We presented only the primary reason for exclusion for each study in the table.

References of studies excluded in full-text screening

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Supplementary Table 3-3. Relative risks and 95% CIs between physical activity (time-varying exposure or averaged exposure) and all-cause, CVD and cancer mortality

Author, year, exposure	Categories	All-cause mortality	CVD mortality	Cancer mortality
Leisure-time physical activity				
Bembom (2009), recent (past 12 months) exposures weighted averages across 4 timepoint-specific estimates ^a	Low (<22.5 METs), age <75	-0.015(-0.031,0.003)		
	High (≥22.5 METs), age <75	-0.007(-0.026,0.011)		
	Low (<22.5 METs), age ≥75	-0.078(-0.130,-0.033)		
	High (≥22.5 METs), age ≥75	-0.102(-0.179,-0.042)		
Huerta (2016), 3.3-year average	Men: <7.5 MET-h/w	1.00	1.00	1.00
	Men: 7.5-14.9 MET-h/w	1.06(0.79,1.42)	1.15(0.64,2.06)	0.96(0.63,1.46)
	Men: 15.0-29.9 MET-h/w	0.96(0.73,1.26)	1.11(0.65,1.91)	0.96(0.66,1.40)
	Men: ≥30 MET-h/w	0.96(0.73,1.25)	0.82(0.47,1.43)	0.86(0.59,1.24)
	Women: <7.5 MET-h/w	1.00	1.00	1.00
	Women: 7.5-14.9 MET-h/w	0.75(0.54,1.05)	1.09(0.46,2.58)	0.81(0.50,1.29)
	Women: 15.0-29.9 MET-h/w	0.87(0.65,1.16)	1.18(0.54,2.60)	1.09(0.72,1.65)
	Women: ≥30 MET-h/w	0.71(0.52,0.98)	0.64(0.26,1.58)	0.96(0.62,1.47)
Lissner (1996), adulthood average	Per 1 unit increase in average adulthood activity index	0.42(0.24,0.74)	0.36(0.08,1.59)	
Byberg (2009), 35-year time-varying exposure	High	1.00		
	Medium	1.22(1.08,1.37)		
	Low	1.40(1.18,1.66)		
Opdal (2020), Leisure-time, 13-year time-varying exposure	Light PA: None	1.00		
	Light PA: <1 h/w	1.42(0.80,2.53)		
	Light PA: 1-2 h/w	1.22(0.75,1.98)		
	Light PA: >3 h/w	1.03(0.71,1.50)		
	Hard PA: None	1.00		
	Hard PA: Low	0.74(0.58,0.95)		
	Hard PA: Moderate	0.68(0.53,0.86)		
	Hard PA: Vigorous	0.64(0.55,0.75)		
Kaplan (1996), 18-year time-varying exposure	Per four-point increase in the 12-point PA scale	0.84(0.77,0.92)	0.81(0.71,0.93)	
Myers (2004), lifetime exposure	Recreational activity/week, lifetime	0.68(0.49,0.95)		
Joseph (2020), 27-year time-varying exposure	Inactivity	1.00		
	Light activity	0.76(0.64,0.91)		
	Moderate activity	0.68(0.56,0.84)		

Supplementary Table 3-3. Relative risks and 95% CIs between physical activity (time-varying exposure or averaged exposure) and all-cause, CVD and cancer mortality (continued)

Author, year, exposure	Categories	All-cause mortality	CVD mortality	Cancer mortality
Embersson (2005), 20-year average	None	1.00		
	Occasional	0.62(0.52, 0.74)		
	Light	0.45(0.37, 0.54)		
	Moderate	0.38(0.31, 0.47)		
	Moderately vigorous	0.31(0.25, 0.40)		
	Vigorous	0.41(0.31, 0.55)		
Sheehy (2020), 20-year time-varying exposure	None	1.00	1.00	1.00
	0–<7.5 MET h/w	0.75(0.69, 0.81)	0.79(0.68, 0.92)	0.86(0.75, 0.99)
	7.5–<15 MET h/w	0.62(0.56, 0.69)	0.57(0.46, 0.70)	0.76(0.64, 0.91)
	15–<30 MET h/w	0.56(0.51, 0.62)	0.54(0.44, 0.65)	0.69(0.58, 0.81)
	≥30 MET h/w	0.46(0.41, 0.51)	0.48(0.38, 0.61)	0.54(0.45, 0.65)
Talbot (2007), 1) 38-year time-varying exposure in men; 2) 18-year time-varying exposure in women	Men aged<70: per SD of LTPA (MET-min/24 h)	0.66(0.57,0.75)	0.61(0.49,0.75)	
	Men aged<70: Rate of change in total LTPA	0.86(0.77,0.97)	0.80(0.66,0.97)	
	Men aged≥70: per SD of LTPA (MET-min/24 h)	0.89(0.77,1.04)	0.98(0.79,1.22)	
	Men aged≥70: Rate of change in total LTPA	1.08(0.94,1.24)	1.12(0.91,1.38)	
	Women aged<70: per SD of LTPA (MET-min/24 h)	0.68(0.47,0.97)		
	Women aged<70: Rate of change in total LTPA	1.04(0.79,1.37)		
	Women aged≥70: per SD of LTPA (MET-min/24 h)	0.77(0.59,1.03)		
	Women aged≥70: Rate of change in total LTPA	1.03(0.81,1.31)		
Total physical activity				
Hirvensalo (2000), baseline, adjust for recalled past activity	Men: Mobile-Active	1.00		
	Men: Mobile-Sedentary	0.92(0.53,1.59)		
	Women: Mobile-Active	1.00		
	Women: Mobile-Sedentary	0.87(0.55,1.40)		
Hsu (2018), 5-year temporal change	per 1 SD average increase in PASE scores	0.78(0.69,0.88)	0.66(0.55,0.79)	0.92(0.78,1.09)
Stessman (2009), 15-year time-varying exposure	Inactive (< 4 h/w)	1.00		
	Active (≥4 h/w)	0.66(0.46,0.95)		
Yoneda (2020), Various type, Time-varying exposure	Increment of 150 min/w moderate PA	0.72(0.65,0.80)		

Supplementary Table 3-3. Relative risks and 95% CIs between physical activity (time-varying exposure or averaged exposure) and all-cause, CVD and cancer mortality (continued)

Author, year, exposure	Categories	All-cause mortality	CVD mortality	Cancer mortality
Lee (2004), 5-year time-varying exposure	Sedentary	1.00		
	Insufficiently active	0.75(0.62,0.91)		
	Weekend warrior	0.85(0.65,1.11)		
	Regularly active	0.64(0.55,0.73)		
Hamer (2014), 6-year time-varying exposure	Inactivity	1.00	1.00	1.00
	Mild	0.76(0.69,0.83)	0.74(0.64,0.85)	1.02(0.85,1.24)
	Moderate	0.54(0.49,0.59)	0.48(0.41,0.55)	0.86(0.72,1.03)
	Vigorous	0.44(0.39,0.50)	0.46(0.38,0.57)	0.65(0.52,0.81)
Williamson (2019), 8-year hypothetical sustained intervention; 8-year time-varying exposure	Low	1.00		
	Median	0.75(0.67,0.84)		
	High	0.71(0.62,0.81)		
Lantz (2010), 15-year time-varying exposure	Quintile 1 (low)	1.00		
	Quintile 2	0.74(0.49, 1.13)		
	Quintile 3	0.68(0.47, 1.00)		
	Quintile 4	0.73(0.49, 1.10)		
	Quintile 5 of a PA index (high)	0.63(0.48, 0.83)		
Lee (2003), 33-year time-varying exposure	<2100 kJ/week	1.00		
	2100-4199 kJ/week	0.98(0.65,1.49)		
	4200-10499 kJ/week	0.92(0.62,1.35)		
	≥10,500 kJ/week	1.31(0.69,1.92)		
Orsini (2009), lifetime average	Lifetime average <39 MET-h/d			1.00
	Lifetime average 39 to 42.4 MET-h/d			0.96(0.53,1.75)
	Lifetime average 42.5 to 46 MET-h/d			1.02(0.55,1.87)
	Lifetime average >46 MET-h/d			0.98(0.53,1.83)
Stenholm (2015), Adulthood cumulative exposure	Cumulative PA score 0 (inactive at all three ages)	1.00		
	Cumulative PA score 1-2	0.73(0.38, 1.41)		
	Cumulative PA score 3-4	0.77(0.41, 1.45)		
	Cumulative PA score 5-6 (most of the time active)	0.48(0.29, 0.79)		

LTPA: leisure-time physical activity. ^a Reported excess risks weighted over 4 time point specific estimates and compare all-cause mortality in the 2 years following a survey for high PA (≥22.5 METs) with the corresponding risk for low PA (<22.5 METs). Other studies reported hazard ratios.

Appendix B: Supplementary material related to Chapter 5

This section presents supplementary material related to the following publication:

Yi Yang, Pierre-Antoine Dugué, Brigid M Lynch, Allison M Hodge, Amalia Karahalios, Robert J MacInnis, Roger L Milne, Graham G Giles, Dallas R English. Trajectories of body mass index in adulthood and all-cause and cause-specific mortality in the Melbourne Collaborative Cohort Study. *BMJ Open* 2019;9:e030078.doi: 10.1136/bmjopen-2019-030078

Supplementary material

Supplementary Figure 5-1. Flow of participants in the Melbourne Collaborative Cohort Study (MCCS)

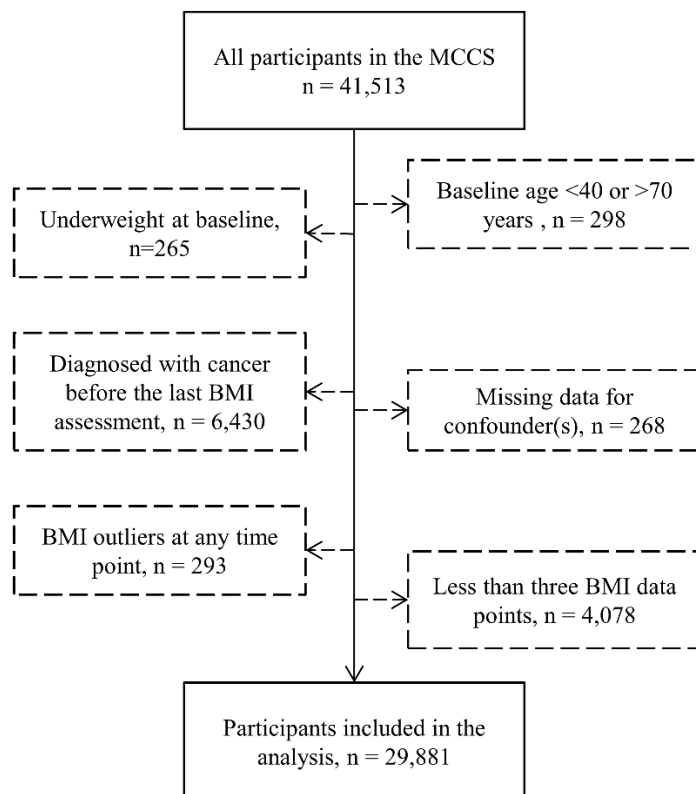
Supplementary Table 5-1. Model adequacy of the selected group-based BMI trajectory model

Supplementary Table 5-2. Hazard ratios for cause-specific mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers

Supplementary Table 5-3. Hazard ratios for cause-specific mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers, excluding participants who did not attend 2003-07 data collection

Supplementary Table 5-4. comparison of model fit, models using BMI trajectories and models using last measured BMI

Supplementary Figure 5-1. Flow of participants in the Melbourne Collaborative Cohort Study (MCCS)



MCCS: Melbourne Collaborative Cohort Study; BMI: body mass index.

Supplementary Table 5-1. Model adequacy of the selected group-based BMI trajectory model

Trajectories	Number of participants	Average posterior probability of assignment	Odds of correct classification	Observed probability	Probability based on the posterior probability
TR 1	5748	0.89	32.79	0.19	0.20
TR 2	11229	0.85	9.11	0.38	0.37
TR 3	8130	0.84	14.17	0.27	0.27
TR 4	933	0.82	137.12	0.03	0.03
TR 5	2893	0.87	62.34	0.10	0.10
TR 6	948	0.94	495.30	0.03	0.03

95% CI around each trajectory is narrow based on visual assessment.

Supplementary Table 5-2. Hazard ratios for cause-specific mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers

BMI trajectory groups	Overall ^a n=(29,881)				Never-smokers ^b n=(17,475)			
	Person-years	Deaths	HR	(95% CI)	Person-years	Deaths	HR	(95% CI)
Obesity-related cancer mortality								
TR1 Lower-normal stable	56,674	109	1.00		35,448	64	1.00	
TR2 Higher-normal stable	112,461	285	1.18	(0.94, 1.48)	65,946	152	1.20	(0.90, 1.62)
TR3 Normal to overweight	82,615	206	1.24	(0.97, 1.57)	46,090	104	1.29	(0.94, 1.78)
TR4 Borderline obesity chronic	9,470	37	1.82	(1.24, 2.68)	4,968	17	1.92	(1.11, 3.32)
TR5 Normal to class I obesity	29,501	76	1.49	(1.10, 2.01)	17,918	43	1.53	(1.02, 2.28)
TR6 Overweight to class II obesity	9,793	33	2.33	(1.56, 3.47)	6,165	18	2.13	(1.24, 3.65)
CVD mortality								
TR1 Lower-normal stable	56,674	234	1.00		35,448	124	1.00	
TR2 Higher-normal stable	112,461	505	0.88	(0.69, 1.13)	65,946	218	0.82	(0.66, 1.03)
TR3 Normal to overweight	82,615	349	0.85	(0.64, 1.12)	46,090	145	0.88	(0.69, 1.13)
TR4 Borderline obesity chronic	9,470	68	1.28	(0.80, 2.03)	4,968	24	1.11	(0.71, 1.74)
TR5 Normal to class I obesity	29,501	138	1.09	(0.77, 1.54)	17,918	64	1.27	(0.93, 1.73)
TR6 Overweight to class II obesity	9,793	43	2.27	(1.34, 3.87)	6,165	23	1.62	(1.02, 2.56)
Other-cause mortality								
TR1 Lower-normal stable	56,674	822	1.00		35,448	418	1.00	
TR2 Higher-normal stable	112,461	1,722	0.88	(0.81, 0.96)	65,946	852	0.97	(0.86, 1.09)
TR3 Normal to overweight	82,615	1,276	0.99	(0.90, 1.09)	46,090	574	1.04	(0.91, 1.18)
TR4 Borderline obesity chronic	9,470	175	1.07	(0.90, 1.28)	4,968	79	1.12	(0.87, 1.44)
TR5 Normal to class I obesity	29,501	389	1.05	(0.92, 1.19)	17,918	211	1.18	(0.99, 1.40)
TR6 Overweight to class II obesity	9,793	111	1.13	(0.92, 1.40)	6,165	66	1.33	(1.01, 1.73)

^a Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline MDS, alcohol drinking status and physical activity score. ^b Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, baseline MDS, alcohol drinking status and physical activity score.

Supplementary Table 5-3. Hazard ratios for cause-specific mortality according to BMI trajectory groups in the Melbourne Collaborative Cohort Study, overall and in never-smokers, excluding participants who did not attend 2003-07 data collection

BMI trajectory groups	Overall ^a n=(21,903)				Never-smokers ^b n=(13,253)			
	Person-years	Deaths	HR	(95% CI)	Person-years	Deaths	HR	(95% CI)
Obesity-related cancer mortality								
TR1 Lower-normal stable	39,926	47	1.00		26,075	29	1.00	
TR2 Higher-normal stable	72,279	130	1.37	(0.98, 1.93)	43,771	65	1.21	(0.78, 1.88)
TR3 Normal to overweight	49,305	80	1.26	(0.87, 1.83)	28,430	42	1.23	(0.76, 2.00)
TR4 Borderline obesity chronic	4,992	19	2.74	(1.57, 4.75)	2,733	12	3.41	(1.69, 6.85)
TR5 Normal to class I obesity	16,787	28	1.46	(0.90, 2.36)	10,462	16	1.36	(0.73, 2.55)
TR6 Overweight to class II obesity	5,258	13	2.58	(1.37, 4.86)	3,510	8	2.26	(1.01, 5.07)
CVD mortality								
TR1 Lower-normal stable	39,926	128	1.00		26,075	68	1.00	
TR2 Higher-normal stable	72,279	208	0.74	(0.59, 0.93)	43,771	97	0.75	(0.55, 1.03)
TR3 Normal to overweight	49,305	140	0.82	(0.64, 1.05)	28,430	72	0.94	(0.67, 1.32)
TR4 Borderline obesity chronic	4,992	27	1.36	(0.89, 2.09)	2,733	14	1.44	(0.79, 2.61)
TR5 Normal to class I obesity	16,787	56	1.32	(0.96, 1.83)	10,462	29	1.23	(0.79, 1.93)
TR6 Overweight to class II obesity	5,258	17	1.55	(0.92, 2.60)	3,510	9	1.43	(0.70, 2.93)
Other-cause mortality								
TR1 Lower-normal stable	39,926	483	1.00		26,075	263	1.00	
TR2 Higher-normal stable	72,279	950	0.91	(0.82, 1.03)	43,771	472	0.94	(0.80, 1.09)
TR3 Normal to overweight	49,305	687	1.10	(0.97, 1.24)	28,430	327	1.14	(0.96, 1.36)
TR4 Borderline obesity chronic	4,992	78	1.08	(0.84, 1.40)	2,733	39	1.03	(0.72, 1.47)
TR5 Normal to class I obesity	16,787	198	1.18	(0.99, 1.41)	10,462	121	1.31	(1.05, 1.65)
TR6 Overweight to class II obesity	5,258	53	1.10	(0.81, 1.48)	3,510	33	1.41	(0.97, 2.05)

^a Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline MDS, alcohol drinking status and physical activity score. ^b Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, baseline MDS, alcohol drinking status and physical activity score.

Supplementary Table 5-4. comparison of model fit, models using BMI trajectories and models using last measured BMI

Model		Trajectories ^a				Last measured BMI ^b			
		ll	df	AIC	BIC	ll	df	AIC	BIC
All-cause	Overall	-36,836	20	73,711	73,877	-36,842	20	73,724	73,890
	Never smokers	-19,284	20	38,607	38,763	-19,289	20	38,618	38,774
Obesity-related cancer	Overall	-4,650	22	9,343	9,526	-4,653	22	9,350	9,533
	Never smokers	-2,779	23	5,603	5,782	-2,780	23	5,606	5,785
CVD	Overall	-984	20	2,007	2,173	-984	20	2,007	2,174
	Never smokers	-4,389	25	8,828	9,022	-4,392	25	8,833	9,027
Other-cause	Overall	-16,883	15	33,795	33,920	-16,886	15	33,803	33,928
	Never smokers	-10,431	16	20,893	21,018	-10,433	16	20,898	21,023

CVD, cardiovascular diseases; ll, log likelihood; df, degree of freedom; AIC, Akaike information criterion; BIC, Bayesian information criterion.

^a Adjusted for age, birth cohort, height, sex, country of birth, SEIFA, highest level of education, smoking status at latest BMI assessment, baseline MDS, alcohol drinking status, and physical activity score. ^b The last BMI measurements were categorised into 6 groups: underweight (BMI < 18.5 kg/m²), lower normal (BMI ≥ 18.5 kg/m² and < 23 kg/m²), higher normal (BMI ≥ 23 kg/m² and < 25 kg/m²), overweight (BMI ≥ 25 kg/m² and < 30 kg/m²), class I obesity (BMI ≥ 30 kg/m² and < 35 kg/m²), and class II obesity (BMI ≥ 35 kg/m²).

Appendix C: Supplementary material related to Chapter 6

This section presents supplementary material related to the following publication:

Yi Yang, Allison M. Hodge, Pierre-Antoine Dugué, Elizabeth J. Williamson, Paul A. Gardiner, Elizabeth L.M. Barr, Neville Owen, David W. Dunstan, Brigid M Lynch, Dallas R English. Mortality effects of hypothetical interventions on physical activity and TV viewing. *Medicine & Science in Sports & Exercise* 2021;53(2):316-323. DOI: 10.1249/mss.0000000000002479.

Supplementary material

Supplementary Figure 6-1. Causal diagram: an example of time-varying confounding affected by prior exposure.

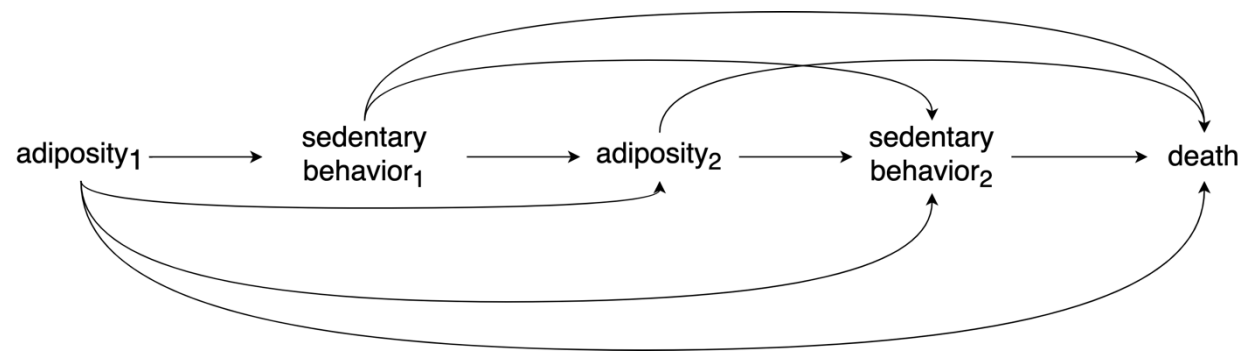
Supplementary Table 6-1. Summary of variables used to model 13-year risk of death

Supplementary Table 6-2. T1 Characteristics of participants attended T2 and participants who were alive but did not attend T2

Supplementary Table 6-3. Estimated risk of death under various modelling orders of time-varying covariates

Supplementary Table 6-4. Pre-baseline (T0) characteristics of participants, by T1 attendance status

Supplementary Figure 6-1. Causal diagram: an example of time-varying confounding affected by prior exposure.



When estimating the effect of *sedentary behavior*₁ and *sedentary behavior*₂ on risk of *death* in a regression model, not conditioning on *adiposity*₂ will lead to unadjusted confounding. However, adjusting for *adiposity*₂ will block some causal pathways from *sedentary behavior*₁ to *death*.

Supplementary Table 6-1. Summary of variables used to model 13-year risk of death

Variables	Categories	Collection wave(s)	Type of model when used as dependent variable	Variables conditioned on in the model	Functional form when used as independent variable
Death between T1 and T2	Yes; No	Linkage	Logistic	All prior values of physical activity and TV viewing time, with an interaction term between the most recent values; past values of all time-varying covariates and comorbidity histories; and all time-fixed covariates.	-
Death between T2 and 14 April 2017	Yes; No	Linkage	Logistic	As above, for participants who are simulated to be alive at T2.	-
Weekly physical activity	< 30 minutes; 30 to 149 minutes; 150 to 300 minutes; > 300 minutes	T0, T1, T2	T0: not predicted T1 and T2: Ordered logistic	As above if not part of a hypothetical intervention; set to an intervening value if part of a hypothetical intervention.	Categories as pseudo-continuous
Daily TV viewing	< 2 hours; 2 to < 4 hours; ≥ 4 hours	T0, T1, T2	T0: not predicted T1 and T2: Ordered logistic	As above, if not part of a hypothetical intervention; set to an intervening value if part of a hypothetical intervention.	3 categories
Sex	Male; Female	T1	Time-fixed, not predicted	-	2 categories
Baseline age	Continuous in years	T1	Time-fixed, not predicted	-	Continuous
The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) quintiles	1 (greatest disadvantage); 2; 3; 4; 5 (greatest advantage)	T1	Time-fixed, not predicted	-	Quintile indicators
Born in Australia/New Zealand	Yes; No	T1	Time-fixed, not predicted	-	2 categories
Level of education	University or technical institution; completed high school; some high school; primary/never attended school	T1	Time-fixed, not predicted	-	4 categories
History of high cholesterol	Yes; No	T0, T1, T2	T0 and T1: not predicted T2: Logistic ^a	For participants simulated to be alive at T2: All prior values of physical activity and TV viewing time, with an interaction term between the most recent values; past values of all time-varying covariates and comorbidity histories; and all time-fixed covariates.	2 categories
History of high blood pressure	Yes; No	T0, T1, T2	T0 and T1: not predicted T2: Logistic ^a	As above.	2 categories
History of heart diseases	Yes; No	T0, T1, T2	T0 and T1: not predicted T2: Logistic ^a	As above.	2 categories

Supplementary Table 6-1. Summary of variables used to model 13-year risk of death (continued)

Variables	Categories	Collection wave(s)	Type of model when used as dependent variable	Variables conditioned on in the model	Functional form when used as independent variable
History of diabetes	Yes; No	T0, T1, T2	T0 and T1: not predicted T2: Logistic ^a	As above.	2 categories
Self-reported general health	Excellent; very good; good; fair; poor	T0, T1, T2	T0 and T1: not predicted T2: Ordered logistic	As above.	Categories as pseudo-continuous
Waist circumference ^b	Normal; increased risk; greatly increased risk	T0, T1, T2	T0 and T1: not predicted T2: Ordered logistic	As above.	3 categories
Mediterranean Diet Score	0 to 3; 3 to 6; 7 to 9	T0, T1, T2	T0 and T1: not predicted T2: Ordered logistic	As above.	3 categories
Smoking status	Never smoker; former smoker; current smoker	T0, T1, T2	T0 and T1: not predicted T2: Logistic	As above. Probability of quitting smoking at T2 was modelled for T1 current smokers. We assumed non-smokers would not start smoking at T2.	3 categories
Alcohol intake (g/day)	0 (Male & Female); 1-39 (Male)/1-19(Female); 40-59(Male)/20-39(Female); 60+(Male)/40+(Female) g/day	T0, T1, T2	T0 and T1: not predicted T2: Ordered logistic	As above.	Categories as pseudo-continuous

^a For these variables, T2 value was predicted based on a logistic regression only if self-reported 'No' at T1. ^b Normal: <94cm (male) or <80cm (female); increased risk: 94cm to <102cm (male) or 80cm to <88 cm (female); greatly increased risk: ≥102cm (male) or ≥88 (women).

Supplementary Table 6-2. T1 Characteristics of participants attended T2 and participants who were alive but did not attend T2

T1 Characteristics	Sample at T1		Attended T2		Did not attend T2	
	n=6377		n=4785		n=1219	
Baseline age (years), mean(SD)	56.5	(12.8)	54.5	(11.4)	59.4	(14.1)
Sex, N(%)						
Male	2891	(45.3)	2120	(44.3)	547	(44.9)
Female	3486	(54.7)	2665	(55.7)	672	(55.1)
Born in Australia/New Zealand, N(%)	4839	(75.9)	3725	(77.8)	843	(69.2)
The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), N(%)						
1 (greatest disadvantage)	1084	(17.3)	725	(15.4)	269	(22.4)
2	1296	(20.7)	937	(19.9)	273	(22.8)
3	1291	(20.6)	967	(20.5)	258	(21.5)
4	1204	(19.2)	940	(20.0)	203	(16.9)
5 (greatest advantage)	1395	(22.2)	1137	(24.2)	196	(16.3)
Level of education, N(%)						
University or technical institution	2561	(40.2)	2109	(44.1)	368	(30.2)
Completed high school	1460	(22.9)	1087	(22.7)	297	(24.4)
Some high school	1966	(30.8)	1413	(29.5)	422	(34.6)
Primary or never attended school	390	(6.1)	176	(3.7)	132	(10.8)
Baseline height(cm), mean(SD)	167.6	(9.6)	168.1	(9.4)	166.2	(9.9)
Weekly Physical activity, N(%)						
< 30 minutes	1099	(17.4)	763	(16.0)	227	(18.9)
30 to 149 minutes	1626	(25.7)	1239	(26.1)	299	(24.9)
150 to 300 minutes	1480	(23.4)	1112	(23.4)	278	(23.1)
> 300 minutes	2118	(33.5)	1642	(34.5)	398	(33.1)
Daily TV viewing time, N(%)						
< 2 hours	3385	(53.6)	2671	(56.1)	579	(48.3)
2 to 4 hours	2340	(37.0)	1707	(35.9)	467	(38.9)
>= 4 hours	595	(9.4)	379	(8.0)	154	(12.8)
Mediterranean Diet Score, N(%)						
0-3	1922	(30.7)	1438	(30.5)	369	(31.1)
4-6	3695	(59.0)	2770	(58.7)	706	(59.5)
7-9	651	(10.4)	513	(10.9)	112	(9.4)
Waist circumference*, N(%)						
Normal	2120	(33.3)	1665	(34.9)	365	(30.1)
Increased risk	1654	(26.0)	1238	(25.9)	312	(25.7)
Greatly increased risk	2584	(40.6)	1871	(39.2)	536	(44.2)

N: number; SD: standard deviation. *Normal, <94 cm (male) or <80 cm (female); increased risk, 94 to <102 cm (male) or 80 to <88 cm (female); greatly increased risk, ≥102 cm (male) or ≥88 (women).

Supplementary Table 6-3. Estimated risk of death under various modelling orders of time-varying covariates

Interventions	13-year risk of death (%), 95% CI	Population risk ratio, 95% CI	Population risk difference (%), 95% CI
Order 1^a			
Natural course	12.3 (11.1 to 13.5)	Reference	Reference
Joint, intensive	10.5 (8.7 to 12.4)	0.86 (0.70 to 1.01)	-1.8 (-3.7 to 0.1)
Order 2^b			
Natural course	12.3 (11.3 to 13.3)	Reference	Reference
Joint, intensive	10.9 (9.0 to 12.7)	0.88 (0.74 to 1.02)	-1.5 (-3.2 to 0.3)
Order 3^c			
Natural course	12.1 (10.9 to 13.2)	Reference	Reference
Joint, intensive	10.5 (8.7 to 12.4)	0.87 (0.73 to 1.01)	-1.6 (-3.3 to 0.2)
Order 4^d			
Natural course	12.0 (10.9 to 13.1)	Reference	Reference
Joint, intensive	10.4 (8.5 to 12.4)	0.87 (0.72 to 1.02)	-1.6 (-3.3 to 0.2)

The observed 13-year risk of death was 12.2%; 200 bootstrap samples were drawn for each of the 40 imputed datasets to estimate the standard errors and 95% CIs.

^aOrder 1: TV viewing, physical activity, high cholesterol, high blood pressure, heart conditions, diabetes, self-reported general health, waist circumference, Mediterranean Diet Score, smoking status, and alcohol intake.

^bOrder 2: Physical activity, TV viewing, high cholesterol, high blood pressure, heart conditions, diabetes, Mediterranean Diet Score, smoking, alcohol intake, waist circumference, and self-reported general health.

^cOrder 3: Physical activity, TV viewing, high blood pressure, high cholesterol, diabetes, heart conditions, Mediterranean Diet Score, smoking, alcohol intake, waist circumference, and self-reported general health.

^dOrder 4: Physical activity, TV viewing, self-reported general health, waist circumference, Mediterranean diet score, smoking, alcohol intake, high cholesterol, high blood pressure, heart conditions, and diabetes.

Supplementary Table 6-4. Pre-baseline (T0) characteristics of participants, by T1 attendance status

T0 Characteristics	Sample at T0		Attended T1		Did not attend T1	
	n=11247		n=6377		n=4847	
Baseline age (years), mean(SD)	51.5	(14.5)	51.5	(12.8)	51.6	(16.4)
Sex, N(%)						
Male	5048	(44.9)	2891	(45.3)	2155	(44.5)
Female	6199	(55.1)	3486	(54.7)	2692	(55.5)
Born in Australia/New Zealand, N(%)	8434	(75.0)	4839	(75.9)	3579	(73.8)
The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), N(%)						
1 (greatest disadvantage)	2241	(20.2)	1084	(17.3)	1155	(24.1)
2	2342	(21.1)	1296	(20.7)	1041	(21.7)
3	2236	(20.2)	1291	(20.6)	939	(19.6)
4	2065	(18.6)	1204	(19.2)	857	(17.9)
5 (greatest advantage)	2203	(19.9)	1395	(22.2)	803	(16.7)
Level of education, N(%)						
University or technical institution	4097	(36.4)	2561	(40.2)	1522	(31.4)
Completed high school	2403	(21.4)	1460	(22.9)	937	(19.3)
Some high school	3935	(35.0)	1966	(30.8)	1966	(40.6)
Primary or never attended school	809	(7.2)	390	(6.1)	419	(8.6)
Baseline height(cm), mean(SD)	168.1	(9.6)	168.5	(9.5)	167.6	(9.8)
Weekly Physical activity, N(%)						
< 30 minutes	2397	(21.5)	1257	(19.9)	1135	(23.7)
30 to 149 minutes	2946	(26.4)	1686	(26.7)	1254	(26.2)
150 to 300 minutes	2395	(21.5)	1368	(21.6)	1025	(21.4)
> 300 minutes	3401	(30.5)	2015	(31.9)	1376	(28.7)
Daily TV viewing time, N(%)						
< 2 hours	6174	(55.3)	3655	(57.7)	2510	(52.4)
2 to 4 hours	4038	(36.2)	2225	(35.1)	1801	(37.6)
>= 4 hours	943	(8.5)	459	(7.2)	482	(10.1)
Mediterranean Diet Score, N(%)						
0-3	3538	(31.5)	1870	(29.3)	1657	(34.2)
4-6	6529	(58.1)	3766	(59.1)	2754	(56.8)
7-9	1180	(10.5)	741	(11.6)	436	(9.0)
Waist circumference*, N(%)						
Normal	4287	(38.7)	2500	(39.6)	1772	(37.5)
Increased risk	2832	(25.6)	1641	(26.0)	1187	(25.1)
Greatly increased risk	3949	(35.7)	2173	(34.4)	1772	(37.5)
Smoking status, N(%)						
Never smoker	6072	(55.0)	3686	(58.8)	2371	(50.0)
Former smoker	3218	(29.2)	1858	(29.6)	1357	(28.6)
Current smoker	1745	(15.8)	723	(11.5)	1017	(21.4)

Supplementary Table 6-4. Pre-baseline (T0) characteristics of participants, by T1 attendance status (continued)

T0 Characteristics	Sample at T0	Attended T1	Did not attend T1
	n=11247	n=6377	n=4847
Alcohol intake (g/day), N(%)			
0 g/day (Male & Female)	1861 (16.5)	940 (14.7)	919 (19.0)
1-39(Male)/1-19(Female)	7894 (70.2)	4571 (71.7)	3303 (68.1)
40-59(Male)/20-39(Female)	1048 (9.3)	627 (9.8)	420 (8.7)
60+(Male)/40+(Female)	444 (3.9)	239 (3.7)	205 (4.2)
Self-reported general health, N(%)			
Excellent	936 (8.4)	603 (9.5)	331 (6.9)
Very Good	3786 (33.9)	2346 (37.0)	1436 (29.8)
Good	4739 (42.4)	2633 (41.5)	2092 (43.5)
Fair	1538 (13.8)	693 (10.9)	843 (17.5)
Poor	184 (1.6)	74 (1.2)	109 (2.3)
History of health conditions, N(%)			
High cholesterol	2832 (25.4)	1714 (27.0)	1116 (23.4)
High blood pressure	3046 (27.2)	1690 (26.6)	1354 (28.1)
Diabetes	567 (5.0)	276 (4.3)	291 (6.0)
Heart conditions	938 (8.4)	443 (7.0)	495 (10.3)

N: number; SD: standard deviation. *Normal: <94cm (male) or <80cm (female); increased risk: 94cm to <102cm (male) or 80cm to <88 cm (female); greatly increased risk: ≥102cm (male) or ≥88 (women).

Appendix D: Supplementary material related to Chapter 7

This section presents supplementary material related to the following manuscript:

Yi Yang, Allison M. Hodge, Brigid M. Lynch, Pierre-Antoine Dugué, Elizabeth J. Williamson, Harindra Jayasekara, Gita Mishra, Dallas R. English. Sustained hypothetical interventions on midlife alcohol consumption in relation to all-cause and cancer mortality in women.

Supplementary material

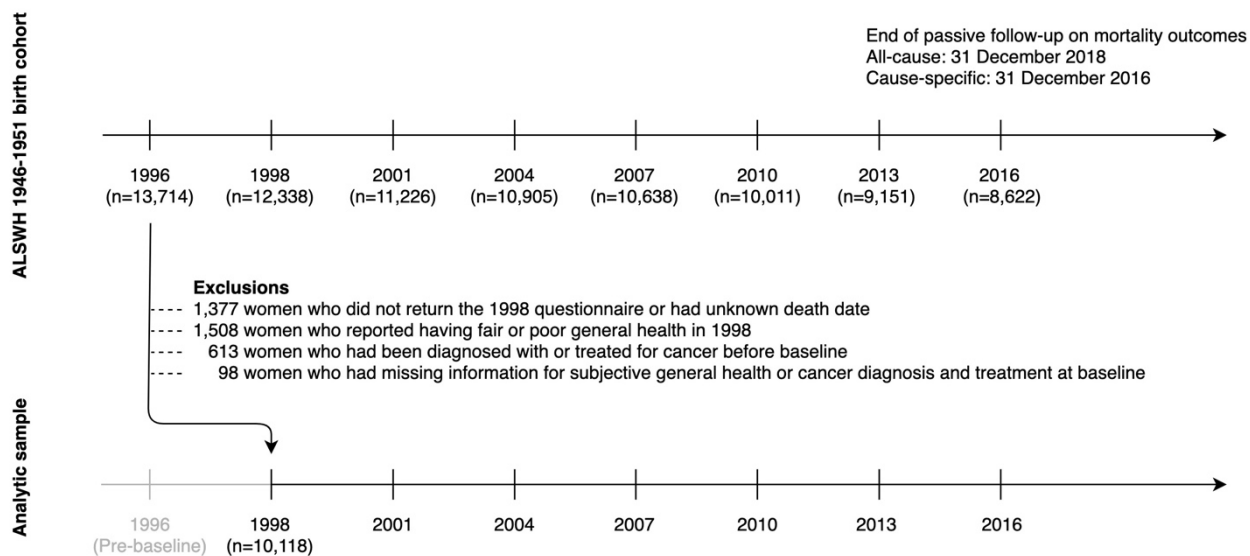
Supplementary Figure 7-1. Timeline of the data collection waves for ALSWH 1946-51 birth cohort

Supplementary Table 7-1. Details of covariates and models in the parametric g-formula

Supplementary Table 7-2. Baseline characteristics of eligible women, by death status

Supplementary Table 7-3. Results from different orders of covariates under each scenario

Supplementary Figure 7-1. Timeline of the data collection waves for ALSWH 1946-51 birth cohort



We used the 1998 wave as baseline to be able to adjust for pre-baseline confounders. In the analytic sample, multiple imputation by chained equation was used to impute missing data due to non-response of follow-up questionnaires or missing responses from respondents.

Supplementary Table 7-1. Details of covariates and models in the parametric g-formula

Variables	Categories	Model when used as dependent variable	Variables conditioned on in the model	Functional form when used as independent variable
Alcohol intake	Continuous in g/day	Logistic model for indicator for any alcohol consumption (>0 g/day), and linear regression model for natural log of intake restricting to records where intake was greater than 0 g/day.	All time-fixed confounders, pre-baseline, and most recent lag value of time-varying confounders, and exposure history	Most recent lag value and cumulative average before it. For example, at time = k: value at k-1, and the average of g/day from time =0 to time=k-2
Death	Indicator	Logistic	As above.	-
Time-fixed confounders				
Age at baseline	Continuous in years	Not predicted	-	Continuous
Australian born, as proxy for cultural exposure	Indicator	Not predicted	-	Indicator
Alcohol at different stage of life: average drink/week in your late teens, 20s, 30s (3 separate variables)	No alcohol; 1-7 drinks; 8-14 drinks; 15+ drinks	Not predicted	-	4 categories
Highest educational qualification	No formal education; higher school certificate; diploma/ university/higher degrees	Not predicted	-	3 categories
Smoked at least 100 cigarettes in total before baseline	Indicator	Not predicted	-	Indicator
Ever diagnosed with depression, heart disease, hypertension, or diabetes before baseline (one variable for each condition)	Indicator	Not predicted	-	Indicator
Time-varying confounders				
Area-based Index of Relative Socio-Economic Disadvantage	Indicator of the most disadvantaged quartile	Logistic	All time-fixed confounders, pre-baseline, and most recent lag of time-varying confounders, and exposure history	Binary indicator

Supplementary Table 7-1. Details of covariates and models in the parametric g-formula (continued)

Variables	Categories	Model when used as dependent variable	Variables conditioned on in the model	Functional form when used as independent variable
Married/de facto	Indicator	Logistic	As above.	Binary indicator
Physical activity	Continuous in weekly metabolic equivalent minutes (METmin/week)	Logistic model for indicator that METmin/week was greater than 0, and linear regression model for natural log of METmins/week restricting to records greater than 0.	As above.	Quadratic function
Cigarettes per day	Continuous in counts	Logistic model for indicator that number was greater than 0, and linear regression for natural log of number restricting to records greater than 0.	As above.	Quadratic function
Vegetable intake (serves/day)	≤ 1 ; 2 to 3; 4; ≥ 5	Ordered logistic	As above.	4 categories
Body mass index	Continuous in kg/m ²	Truncated normal regression with lower bound set to the minimum and maximum values of BMI in the observed dataset plus offset terms ($\pm 0.01\%$).	As above.	Quadratic function
Diagnosed with or treated for depression or anxiety since last survey	Indicator	Logistic	As above.	Indicator
Diagnosed with or treated for any of the following conditions since last survey: heart diseases, hypertension, diabetes, cancer.	Indicator	Logistic	As above.	Indicator
Subjective general health	Indicator of fair or poor health	Logistic	As above.	Indicator

Supplementary Table 7-2. Baseline characteristics of eligible women, by death status

Characteristics	Overall (n=10118)	Alive (n=9549)	Dead (n=569)
Alcohol intake categories, N(%)			
0 g/day	1176(12.7)	1100(12.6)	76(15.2)
>0 to 10 g/day	4815(52.1)	4567(52.2)	248(49.6)
>10 to 20 g/day	1926(20.8)	1841(21.1)	85(17.0)
>20 to 30 g/day	799(8.6)	759(8.7)	40(8.0)
>30 g/day	528(5.7)	477(5.5)	51(10.2)
Age, years, mean(SD)	49.5(1.5)	49.5(1.5)	49.7(1.4)
Born in Australia, N (%)	7688(76.7)	7249(76.7)	439(77.8)
Married or de facto, N(%)	8443(83.9)	7992(84.2)	451(80.0)
Highest qualification, N (%)			
No formal qualification	1570(15.6)	1449(15.3)	121(21.5)
School certificate	4951(49.3)	4678(49.4)	273(48.5)
Diploma/University/Higher degree	3516(35.0)	3347(35.3)	169(30.0)
Area-based Index of Relative Socio-Economic Disadvantage, N(%)			
Most disadvantaged quartile	2391(23.6)	2260(23.7)	131(23.0)
Smoking status, N(%)			
Never	5481(57.6)	5254(58.4)	227(43.2)
Former	2546(26.7)	2424(26.9)	122(23.2)
Current	1495(15.7)	1319(14.7)	176(33.5)
Cigarettes per day for current smoker, n/day, median (IQR)	20.0(12.0,25.0)	20.0(12.0,25.0)	20.0(15.0,30.0)
Physical activity, N(%)			
Very low (0 to <33.3 METmin/week)	1471(15.8)	1372(15.6)	99(19.7)
Low (33.3 to <500 METmin/wk)	2626(28.3)	2487(28.3)	139(27.7)
Moderate (500 to <1000 METmin/wk)	2219(23.9)	2113(24.1)	106(21.1)
High (>=1000 METmin/wk)	2965(31.9)	2807(32.0)	158(31.5)
Body mass index, kg/m ² , mean(SD)	26.1(5.1)	26.1(5.1)	26.7(5.7)
Subjective general health, N(%)			
Excellent	1485(14.7)	1429(15.0)	56(9.8)
Very good	4375(43.2)	4146(43.4)	229(40.2)
Good	4258(42.1)	3974(41.6)	284(49.9)
Ever had the following conditions, N(%)			
Depression or anxiety	1023(10.1)	967(10.1)	56(9.8)
Heart diseases	55(0.5)	49(0.5)	6(1.1)
Hypertension	841(8.3)	782(8.2)	59(10.4)
Diabetes	82(0.8)	76(0.8)	6(1.1)

Abbreviations: SD, standard deviation; IQR, inter-quartile range; MET, metabolic equivalent.

Supplementary Table 7-3. Results from different orders of covariates under each scenario

Interventions	All-cause Mortality Risk, per 1000 women (95%CI)			Cancer Mortality Risk, per 1000 women (95%CI)		
	Main model	Order A	Order B	Main model	Order A	Order B
No intervention	56.0(49.8,62.2)	55.8(49.7,61.9)	55.7(49.6,61.8)	28.1(23.7,32.4)	28.1(23.9,32.2)	27.8(23.7,31.9)
0g/day	63.6(41.6,85.7)	63.6(41.5,85.6)	63.5(41.4,85.5)	26.9(16.6,37.2)	26.9(16.9,36.9)	26.8(16.8,36.8)
>0 to 10 g/day	53.6(46.5,60.7)	53.3(46.3,60.4)	53.3(46.2,60.5)	27.1(22.1,32.0)	27.1(22.3,31.9)	27.0(22.3,31.8)
>10 to 20 g/day	46.4(37.3,55.5)	46.2(37.3,55.1)	46.1(37.2,55.1)	25.3(18.8,31.7)	25.2(18.9,31.5)	25.2(18.9,31.5)
>20 to 30g/day	46.0(35.1,57.0)	45.8(35.1,56.6)	45.8(35.1,56.6)	28.7(20.2,37.3)	28.7(20.4,37.1)	28.7(20.3,37.0)
>30 g/day	63.2(44.6,81.8)	63.0(44.8,81.3)	62.9(44.8,81.1)	32.2(20.2,44.2)	32.2(20.5,43.9)	32.1(20.5,43.7)
Reduce to $\leq$ 20 g/day if higher	52.9(47.0,58.7)	52.7(47.0,58.5)	52.6(46.8,58.3)	27.3(23.1,31.5)	27.4(23.4,31.4)	27.2(23.3,31.2)

Ordering of covariates: Main Model - Alcohol, socioeconomic disadvantage, marital status, lifestyle factors (physical activity, daily number of cigarettes, vegetable intake, body mass index), health (comorbidities and subjective health); Order A - Alcohol, socioeconomic disadvantage, marital status, health, lifestyle factors; Order B - Alcohol, health, lifestyle factors, socioeconomic disadvantage, marital status.