The impact of physical activity and blood pressure on cardiovascular events and mortality

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ABSTRACT

The impact of physical activity and blood pressure on cardiovascular events and mortality

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Hypertension is the leading risk factor for the development of cardiovascular disease (CVD). Physical activity (PA) is beneficial for preventing hypertension and decreases risk of mortality and CVD. The purpose of this thesis was to study the relationships between PA, blood pressure (BP), and how they act to impact mortality and CVD development.

A systematic review examined the impact of PA on mortality in patients with high BP. Six articles evaluating over 90,000 participants were identified. C and all-cause mortality were shown to be inversely related to PA in all studies. Individuals with high BP who participated in any level of PA had a reduced risk of CVD mortality, and greater than two-fold increased risk of mortality was noted for inactive individuals.

The second study specifically examined the main and interaction effects of different levels of PA and BP on both fatal and non-fatal CVD events, and mortality in the Scottish Health Survey. We found a significant interaction effect between PA and BP on CVD such that doing any level of activity for the BP groups <160 mmHg reduced risk of CVD; in those with systolic BP ≥160 mmHg, there was no change in risk.

The third study evaluated the causal relationships between PA, BP, and mortality and Major Adverse Cardiovascular Events (MACE) using the Honolulu Heart Program. Advanced statistical models (i.e., Marginal structural models) were used to estimate the separate causal relationships of PA and BP on mortality/MACE, and the causal relationship of PA on BP. Being active was associated with reduced risk of mortality and MACE. BP was shown to have a dose-dependent relationship with all-cause mortality and MACE (increased BP increased risk of events). Active participants showed a reduced BP (~2.5 mmHg). Being physically active is associated with better outcomes and that BP may be a mediator of this relationship.

The findings from this thesis suggest a causal relationship between greater PA and lower BP, and that high PA acts with low BP in reducing the risk of mortality and cardiovascular events. This outcome supports engagement in physical activity for longevity and maintenance of healthy blood pressure.

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I would like to extend my sincerest gratitude to Anastasia Dikareva for her dedication to working on the systematic review and Dr. Denis Talbot who was instrumental

in bringing the Honolulu Heart Program project to fruition. To my friends and colleagues at the Montreal Behavioural Medicine Centre, thank you. Dr. Gregory Moullec, Maxine Boudreau and Ariane Jacob-Lessard, I cannot express how wonderful it is to have friends like you.

I am very grateful to the funding agencies that have supported my work throughout my doctoral studies; Canadian Institutes of Health Research for entrusting me with the honor of being among the first class of Vanier Canada Graduate Scholars and also for the Michael Smith Foreign Study Supplement, which supported my studies in the UK. I would also like to thank the Fond de recherché- Santé for the Doctoral Training Award. I would also like to gratefully acknowledge Concordia University, the Department of Exercise Science, School of Graduate Studies, Montreal Heart Institute, and various organizations who have supported me through internal awards, teaching positions, and funding for national and international conferences.

Despite always being on the move during my graduate studies, hopping from Denmark, to England, to Australia and back, I have always had a place to call home. I began my undergraduate studies at Concordia University in September 2003. Throughout my twelve years, in the Department of Exercise Science I have come to know many wonderful people; people who were once my teachers, are now some of my greatest friends. I cannot thank them enough from the bottom of my heart for making this experience so rewarding. Dr. Robert Boushel, I genuinely would not have come this far without you. I am so honored for all the experiences you gave me during my Masters, which inspired me to pursue doctoral studies. Your passion and enthusiasm for research are unparalleled. I am so proud

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I cannot conclude the experience of my doctoral studies without acknowledging the opportunities I have had at Concordia University outside of my research experience. I approached Dr. Graham Carr early in 2011 with a project I wanted to undertake; building the Concordia University chapter of Let's Talk Science. Graham wholeheartedly supported my efforts, both financially and with his time. Graham, I cannot thank you enough for allowing me to bring Let's Talk Science to our University, for including me in other University engagements to represent Let's Talk Science, and for your trust. I also must thank Isabel Deslauriers, National Coordinator at Let's Talk Science, for believing in me to take on the task of starting a new site. There is an enormous amount of work and time put into this organization and Isabel is at the epicentre of it all. Without her efforts, the Concordia University Let's Talk Science site would not have been possible. On behalf of all the students and youth we reach, thank you for everything you do.

I genuinely feel that I would not be in this position today if it had not been for all the mentors who influenced me throughout my early years. I must acknowledge Mr. Eugene

Diachyshyn, my science teacher and first thesis mentor during my time in the International Baccalaureate Program at Bishop Whelan High School. His teachings (and very cool disections) ignited my curiosity and passion for the cardiovascular system. I thank Mr. Tony Bambace, my high school math teacher, who encouraged all his students to "dream in technicolour" and I am so grateful he did. Mr. Alain Rodrigue- your enthusiasm for life and passion for teaching is unrivaled. I hope to inspire students one day as you did for me. And to all the elementary and high school teachers at Bishop Whelan whose classrooms I had the privilege to sit in... Thank you.

I dedicate this thesis in part to my family. To my parents, Emilia and Andre, who have supported me every single step of the way and have made infinite sacrifices for myself and my sister. They have always emphasized the importance of education and community, taught us to work hard, to be ambitious, and how to overcome adversity. I owe all my success to them. To my lil'sister, Mariann, who is wise beyond her years and generous to fault. Thank you for always being you and reminding me not to take myself so seriously. Even though I am the "big sister," I look up to you and I am so proud of all that you have accomplished. To my four-legged, canine sister, Mila; you bring such joy to our lives and are a daily reminder of how to love unconditionally. I cannot imagine life without you. To my grandparents who had the audacity to leave their home in search of a better life. Everything I have accomplished is because of your courage. Thank you all for your support, encouragement, and love.

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supporting me not only though my academic endeavours, but also through my personal ventures. Thank you for helping me build our home together. Thank you for helping me persevere, for always loving me, and for reminding me of my own greatness when I forget. I am forever grateful to have you in my life. And so, I also dedicate this thesis to you.

“**Anchora Imparo”**

- Domenico Giunti

DETAILS OF PUBLICAITONS & CONTRIBUTION OF AUTHORS

The major part of this thesis consists of three manuscripts, each at difference phases of the publication process. In addition, several other publications resulting from work throughout my Doctoral training have been appended. Below I provide details of each publication and the role each author played in the paper.

Chapter 2: The impact of physical activity on mortality in patients with high blood pressure: a systematic review

This systematic review was published in 2012 (Rossi *et al*. *Journal of Hypertension* 2012, 30:1277–1288). As the lead author, I was involved in all aspects of this undertaking; conception and design, literature search, data entry, analysis, and interpretation, writing the manuscript and contribution of intellectual content. Ms. Anastasia Dikareva, MSc was implicated in the literature search, data entry and analysis, and revising the manuscript. Drs. Bacon and Daskalopoulou were instrumental in the conception of the project, interpretation of the results, and critical revision of the manuscript. Giuliano Rossi, BSc, assisted with the update and was implicated in the screening of the manuscripts. This update was completed in June 2015 and has been included at the end of Chapter 2. Appendix A is a reprint of the published manuscript and the copyright permission form.

Chapter 3: Association of blood pressure and physical activity on cardiovascular and all-cause mortality: The Scottish Health Survey

This manuscript is based on a large cohort study; the Scottish Health Survey. Thanks to funding from CIHR (Michael Smith Foreign Study Supplement) I was privileged to work under the direction of Dr. Hamer for one summer during my PhD at the Department of Epidemiology and Public Health, University College London, London, UK. During this time I conceived this study which further develops the findings of the systematic review (Chapter 1). My principal role was building the framework for the analysis, conducting analyses and interpretation of the data and statistical analyses. Additionally, I prepared the manuscript and contributed significantly to the scientific content. Drs. Stamatakis and Hamer are responsible for the dataset. Drs. Bacon, Stamatakis, and Hamer all contributed to the conception of this work, as well as making critical revision to the manuscript herein. This manuscript has been submitted to the *Journal of Human Hypertension*. Please see Appendix H for submission confirmation.

Chapter 4: Marginal structural models for estimating the causal relationship between physical activity, blood pressure, and mortality: the Honolulu Heart Program

This final manuscript is an analysis of the Honolulu Heart Program cohort investigating the causal relationships between physical activity, blood pressure and mortality. Dr. Bacon and I conceived and designed this project. I was responsible for designing the DAG models and was implicated in the building of the statistical models (structural equation models, and marginal structural models). Drs. Talbot, Lefebvre, and

Atherton are responsible for the statistical analysis; notably, designing the statistical model and coding the analyses. I have drafted the manuscript, with contributions from Dr. Talbot, and all co-authors have reviewed the document and consented to the contents. You will note that there is a main manuscript and a sizable online supplement at the end of the manuscript. The paper has been constructed this way due to the word limits of the journal it was submitted too. This manuscript has been submitted to *Heart* (see Appendix G for confirmation of submission).

In addition to this main study, two methodological papers have emerged. Appendix B and C are a manuscript (Talbot *et al. Statistics in Medicine* 2015; 34:812-823) and response to commentary (Talbot *et al. Statistics in Medicine* 2015; 34: 2676-2677) , both published in *Statistics in Medicine*. Appendix D is a manuscript in preparation for submission to *Epidemiology*. These pieces formed part of Dr. Talbot's Doctoral thesis.

Appendix E is an original meta-analysis of randomized controlled trials examining the impact of resistance training on resting blood pressure (Rossi *et al. Can J Cardiol* 2013, 29:622-627). This manuscript was published in the Canadian Journal of Cardiology Special Issue on Hypertension. I was responsible for the conception of this project, all data collection and analysis, as well as the main author of the written works. Dr. Gregory Moullec assisted with screening records and conducted the statistical analyses; Gabrielle Gour-Provençal assisted with the literature search and screening records; Dr. Bacon was also part of the conception of this work, and both Drs. Lavoie and Bacon have contributed to the preparation of the manuscript and scientific content. Several conference presentations and abstracts were published based on this project. Appendix F is a Letter to the Editor of Hypertension (Rossi *et al. Hypertension* 2012, 59:e22-23) with commentary on a meta-

analysis on the theme of resistance training and blood pressure. Myself and Dr. Moullec were responsible for the drafting of this letter and all authors contributed to the scientific content.

Appendix I includes a published manuscript (Rossi *et al. Obesity* 2013, 21:E143-148). This is a sub-study of the larger Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia (MOSMI) trial. Ms. Davies and I equally contributed to the work of this manuscript including data and statistical analysis and preparation of the manuscript. I have presented the results at local and national conferences. Dr. Gordon and Mr. Meloche were responsible for data collection and entry. Drs. Arsenault, Lavoie, and Bacon were the Principal Investigators of this study and were responsible for the conception and funding of the project. Dr. Bacon was also responsible for the statistical analysis. All authors reviewed the manuscript for scientific content prior to publication.

Appendix J consists of a second manuscript published in collaboration with this group (Hamer *et al*. *Arterioscler Thromb Vasc Biol* 2012, 32:500-505). I was responsible for the analysis of accelerometry (Actigraph) data, revised the manuscript, and contributed to the scientific content. Drs. Hamer, Venuraju, Lahiri, and Steptoe were responsible for the conception and overseeing data collection, as well as the scientific content. Dr. Hamer was also responsible for the statistical analyses and drafting the manuscript. I also published an abstract and presented a poster on these data at the Canadian Society for Exercise Physiology Annual General Meeting, Québec City, Québec, 2011.

Please note that in accordance with the Concordia University Thesis Regulations, one reference list is provided at the end of the thesis rather than at the end of each chapter.

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LIST OF ABBREVIATIONS

ANS	Autonomic Nervous System
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CV	Cardiovascular
CVD	Cardiovascular Disease
D&B	Downs and Black assessment tool
DAG	Directed Acyclic Graph
DBP	Diastolic Blood Pressure
HPA	High physical activity
HR	Hazard Ratio
ICD	International Classification of Diseases
IL-6	Interleukin-6
LPA	Low physical activity
LIFE	Losartan Intervention for Endpoint
MACE	Major Adverse Cardiovascular Event
Meds	Medications
METs	Metabolic Equivalents
MONICA	Multinational Monitoring of trends and determinants in

	Cardiovascular disease
MPA	Moderate physical activity
MSCM	Marginal structural Cox model
MSM	Marginal structural model
NHANES	National Health and Nutrition Examination Survey
PA	Physical Activity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
Ref	Reference Group
RR	Relative Risk
RT	Resistance Training
SHS	Scottish Health Survey
SBP	Systolic Blood Pressure
TNF-α	tumor necrosis factor-α

CHAPTER 1 | INTRODUCTION

GENERAL INTRODUCTION

HYPERTENSION

Hypertension represents the highest proportion of attributable mortality amongst all global risk factors and is a large burden to health care systems worldwide.(1-3) Reports from 2003 and 2004 indicated that 27% of the Canadian population was affected by hypertension and the prevalence was higher in men (31%) when compared to women (24%).(4, 5) More recent data from the Canadian Health Measures Survey demonstrated that nearly one-fifth of Canadian adults (20-79 years old) have hypertension and that the prevalence of hypertension increases with age for both sexes.(6) Yet, a Canadian retrospective population-based study, that included 26 million Canadians, found that despite decreased incidence of hypertension over ten years (1998-2008), the prevalence of hypertension was increasing.(7) In 2010, the health care costs Canada attributed to hypertension were estimated at $13.9 billion (CAD), and they are projected to increase to $20.5 billion (CAD) by the year 2020.(8) Thus, hypertension affects a large portion of the population and is a huge public health burden.

While only a small portion (~ 2-5%) of patients can identify their hypertension as a secondary effect of adrenal or renal disease (i.e., secondary hypertension), the remaining majority of patients having essential hypertension, which has no singular attributable cause.(9) Many physiological factors have been linked to the etiology of hypertension, including the renin-angiotensin system, the autonomic nervous system (ANS), endothelial dysfunction, vasoactive substances, insulin sensitivity, as well as genetic factors, and

behavioural factors.(9, 10) There is also an association between arterial pressure and inflammatory cytokines which may additionally interact with these other factors.(11) Hypertension is also strongly associated with other co-morbidities, for example obesity,(12) and increased blood pressure (BP) is directly related to a higher risk of stroke, ischemic heart disease, and all-cause mortality (13).

The key elements to managing hypertension are first and foremost appropriate measurement of blood pressure and subsequently, proper diagnosis. Each year the Canadian Hypertension Education Program updates evidence-based recommendations for blood pressure measurement and diagnosis criteria for hypertension, as well as prevention and treatment of hypertension.(14) Various devices have been validated and recommended for use for different types of methods of BP measurement.(15) These methodologies include office BP measurement (by auscultation or automated), ambulatory BP monitoring, and home BP monitoring. Whilst it is beyond the scope of this thesis to evaluate blood pressure measurement techniques and protocols, it is important to acknowledge and understand that these updates are essential in the process of hypertension diagnosis and care. For example, evidence has shown that poor adherence to proper auscultatory protocol for office blood pressure measurement often over-estimates blood pressure compared to automated devices, which can result in improper diagnosis and possibly unnecessary (or misuse of) pharmacological treatment to achieve target blood pressure.(16, 17) In contrast to clinical practice, most research studies normally have well defined higher quality protocols for assessing blood pressure.(17) However, it should be noted that these protocols often differ to some degree and that these difference may have implications for the interpretation of the

results. For example, study protocols may vary in the number of measurements taken or have different operators taking measurements, taking measurements from one arm vs. both arms, etc., all of which are factors pertinent to the accuracy of blood pressure measurement.(18) Also, some studies will use a self-report of physician reported hypertension diagnosis or prescription of hypertensive medications to define the presence of hypertension as this is convenient when using large samples. It is important to bear in mind these differences when interpreting reported results.

Cut-offs for blood pressure classification and target blood pressure vary between organizations.(19-21) Despite nuances in the classification of stages or grade of hypertension, these is concurrence that a standard office-like measurement of 140/90 mmHg is the blood pressure cut-point for non-comorbid hypertension.(20, 21)

PHYSICAL ACTIVITY

Habitual leisure time physical activity has been associated with a reduction in all-cause mortality in both men and women.(22) For example, in one of the first studies of its kind, data from Harvard alumni showed that those who engaged in regular physical activity lived over a year longer than their sedentary counterparts.(23) Furthermore both leisure time physical activity and occupational activity have shown similar results with respect to reducing risk of death from ischemic heart disease.(24) A review of 44 papers concluded that the volume of physical activity and all-cause mortality are related in an inverse, linear

dose-dependent manner.(25) However, some data suggests that moderate intensity exercise is as good, if not better, than high intensity for certain conditions.(26)

Part of the problems of disentangling the physical activity intensity-outcomes relationships is tied to the type and quality of measurement of physical activity. Researchers have extensively studied and compared various subjective and objective measurement tools in order to enhance the quality of data collection and optimise our understanding of the optimal pattern of physical activity.

Subjective Measurement of Physical Activity.

Traditionally, the most common way to assess physical activity has been via the use of subjective measures. Subjective measures mainly include self-report of physical activity, through recall questionnaires, structured interview, or physical activity diaries. Although such methods of data collection are convenient and inexpensive for acquiring information from large cohorts, they can be somewhat burdensome and time consuming for the participants. One key flaw of self-report measures of physical activity is that any information collected is subject to 'recall bias' and may be influenced by the participants' health, mood, depression, and other psychological factors.(27) Another limitation is the difficulty of these tools to accurately determine specific exercise parameters; frequency, duration, intensity, and volume. These elements are important for determining the optimal physical activity "dose" and establishing recommendations for physical activity. Elimination of semantic descriptions of exercise intensity and simplification of the language used in self-report measures to describe the physiological changes related to

exercise intensity (e.g., using cues like “exercise inducing sweating and limiting conversation”) have improved reporting but are still vulnerable to personal interpretation.(28) However, some studies have shown that subjective measures more accurately reflect vigorous physical activity as compared to light or moderate activities.(29-31) It has been suggested that a mix of methods measuring physical activity, fitness and sedentary time may be advantageous for assessing cardiometabolic risk.(32) Each method of data collection has both pros and cons in terms of cost, resource requirements, patient burden, etc. As such, it is difficult to determine which method should prevail. Researchers should pick the most appropriate methods to answer their research questions within their limits of time, money, and manpower.

Physical Activity and Blood Pressure

Current guidelines recommend regular physical activity as a preventative measure and a first-line non-pharmacological treatment for hypertension.(2, 20, 33-35) These recommendations are built form a wealth of evidence that has been accumulated over the last 40 years. For example, recent meta-analyses examining the BP-reducing effect of chronic aerobic exercise training in randomized controlled trials (RCTs) have shown positive results, with an overall decrease of approximately 3-4 mm Hg for SBP and 2-3 mm Hg for DBP.(36, 37) A meta-analysis of epidemiological studies consistently found physical activity and risk of hypertension was inversely related, in a dose-dependent manner.(38)

As previously mentioned, low physical activity and high blood pressure are associated with a greater probability of all-cause mortality and CVD events.(39) Though there is an abundance of literature demonstrating the blood pressure lowering effects of physical activity and exercise, the links between these relationships and longer-term health outcomes have not been extensively studied. There is uncertainty about the mechanisms by which both physical activity and blood pressure impact CVD and mortality despite the associations previously reported. For example, "are there mortality and CVD benefits of increased physical activity in patients with hypertension?" A question which has never been systematically assessed within the literature. If there are benefits in this kind of population, are these benefits equivalent to normotensive individuals, or does one group gain more from engaging in physical activity? Although certain patterns of physical activity are associated with higher cardiorespiratory fitness, which in turn are related to mortality, there is debate about whether physical activity or cardiorespiratory fitness is a better indicator of health,(40, 41) Keeping this in mind, Blair and colleagues have shown that men with higher cardiorespiratory fitness have a decreased risk of mortality, and this is true for both normotensive and hypertensive individuals.(42) To our knowledge, no single study has simultaneously assessed the physical activity-outcomes relationship across blood pressure groups and hypertension status.

Though there is a multitude of RCT data showing blood pressure reductions to increased physical activity, none of the studies have been powered to look at mortality or CVD outcomes.(37) Thus, assumptions regarding the causal role of physical activity to reduce blood pressure and subsequently influence CVD and mortality are purely

speculative. When we consider the existing epidemiological studies on physical activity and hypertension, few have considered this relationship in the context of causal mechanisms to reduce outcomes (CVD and death).(39, 43) However, advanced statistical techniques applied to complex epidemiological studies which include multiple follow-up measures, can allow us to gain perspective on causal relationships. For example, Marginal structural models (MSM) can adjust for time-varying confounders using inverse-probability weighting.(44) This class of statistical models allows researchers to draw causal inferences from observational data. Given the information above, it is clear that there is still much we do not understand about how physical activity and blood pressure interact to reduce overall mortality and cardiovascular disease development.

Of note, several meta-analyses have been conducted on the theme of resistance training and BP.(45-47) Cornelissen et al.(46) found a decrease of 3.9/3.9 mm Hg in participants with normal or prehypertensive BP as well as a decrease of 4.1/1.5 mm Hg in hypertensive individuals who participated in dynamic and isometric resistance training. However, several methodological details of Cornelissen et al.(46) meta-analysis should be considered when interpreting these findings. As previously noted, the study included trials that did not focus on BP as a primary end point and also included isometric handgrip exercise.(47, 48) The inclusion of studies where BP is not the primary end point is potentially problematic, because meta-analyses that do not exclusively consider primary outcomes are more likely to be subject to outcome reporting biases which can influence effect estimates.(49-51) In our own meta-analysis evaluating the impact of resistance training on blood pressure (Appendix E, (47)) we addressed some of the methodological

issues of Cornelissen et al.(46). Most notably, we included only studies which focused on change in resting blood pressure as the main outcome of interest, and, in addition, we excluded isometric resistance training trials. The results showed a significant decreased of ~ 2 mmHg in DBP, but no significant change in SBP.(47) These results are less optimistic than those of Cornelissen et al.(46) in that resistance training was not shown to have a blood pressure lowering effect. Given the inconclusive nature of the relationship between resistance exercise and blood pressure, the current thesis only focuses on aerobic exercise.

AIMS, OBJECTIVES, & HYPOTHESES

Though studies have evaluated the associations between physical activity, blood pressure, and mortality, none have formally examined the causal relationships. Thus, the ultimate aim of this thesis was to investigate the causal relationships between physical activity, blood pressure and all-cause mortality and cardiovascular disease development.

In order to evaluate the existing literature on this theme, we have conducted a systematic review of literature. In doing so, we not only acquire a sense of how these variables relate, but we can also identify gaps in the literature and assess the quality of the publications in a methodically sound scientific manner.

Objective #1: To systematically review the existing literature exploring the relationship(s) between physical activity and mortality (all-cause and cardiovascular) in patients with high blood pressure.

Based on the findings from the systematic review, we designed the subsequent studies to address shortcomings of the published literature. For example, the studies assessed in the systematic review were all designed using association models and did not including any interactions between physical activity and blood pressure. Also, most studies looked at only two levels of physical activity (active vs. inactive). Moreover, none of the studies included cardiovascular events as their outcome; only cardiovascular deaths. In an attempt to resolve some of these limitations we designed the second study, an analysis of the Scottish Health Survey.

Objective #2: To examine the main and interaction effects of physical activity and blood pressure/hypertension status on all-cause mortality and fatal and non-fatal cardiovascular events;

Our hypotheses for this objective were that there would be:

2a) A main effect of physical activity on both all-cause mortality and cardiovascular events such that increasing physical activity would decrease risk of both outcomes.

2b) A main effect of (systolic and diastolic) blood pressure on both all-cause mortality and cardiovascular events, demonstrating a direct and dose-dependent relationship, such that increased blood pressure would be related to increased risk of both outcomes.

2c) An interaction effect between physical activity and blood pressure on both all-cause mortality and cardiovascular events, indicating a multiplicative effect, such that higher levels of physical activity and lower levels of blood pressure would lead to the greatest reductions in risk of mortality and CVD events.

After investigating the interactions between physical activity and blood pressure and assuming that our hypotheses were correct, the next step was to hone in on the potential causal relationships pertaining to mortality and CVD. In order to do so, we designed the next study using a dataset with measurements of physical activity, blood pressure, and covariates at different time points. This allowed us to incorporate the time-varying element of physical activity and blood pressure in order to evaluate the evolution of their relationship with respect to mortality and cardiovascular events.

Objective #3: To investigate the causal relationship between (a) physical activity and blood pressure; (b) physical activity and all-cause and cardiovascular mortality; and (c) blood pressure and all-cause mortality and cardiovascular mortality;

Our hypotheses for this objective were that:

3a) Physical activity would demonstrate a negative causal relationship such that increased physical activity would decrease blood pressure.

3b) Physical activity and both all-cause and cardiovascular mortality would demonstrate causal relationship such that increasing physical activity would decrease risk of both outcomes.

3c) Blood pressure and both all-cause and cardiovascular mortality would demonstrate causal relationship such that increase blood pressure would increase risk of both outcomes.

CHAPTER 2 | THE IMPACT OF PHYSICAL ACTIVITY ON MORTALITY IN PATIENTS WITH HIGH BLOOD PRESSURE: A SYSTEMATIC REVIEW

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See Apendix A for the original article and copyright permission.

ABSTRACT

Physical activity has been shown to be beneficial for the prevention and management of hypertension. In the general population, physical activity has been shown to decrease mortality. **Purpose:** The purpose of this systematic review was to identify and synthesize the literature examining the impact of physical activity on mortality in patients with high blood pressure (BP). **Methods:** An extensive search was conducted by two independent authors using Medline, Embase and Cochrane Library electronic databases (between 1985 and January 2012) and manual search from the reference list of relevant articles. Inclusion criteria were as follows: (1) longitudinal design with minimum 1 year follow-up; (2) hypertensive status of the cohort was indicated; and (3) BP, physical activity, and mortality were measured. **Results:** Six articles evaluating a combined total of 48,448 men and 47,625 women satisfied the inclusion criteria. Cardiovascular and/or all-cause mortality were shown to be inversely related to physical activity in all studies. For example, patients with high BP who participated in any level of physical activity had a reduced risk (by 16%-67%) of cardiovascular mortality, while a greater than two-fold increase in risk of mortality was noted in non-active individuals. However, activity classification and parameters, such as frequency, duration, intensity, and volume, as well as blood pressure status were not consistent across studies. **Conclusions:** Regular physical activity is beneficial for reducing mortality in patients with high BP. More research is needed to establish the impact of specific kinds of physical activity and whether any differences exist between sexes.

Keywords: Physical Activity, Mortality, Blood Pressure, Hypertension, Systematic Review

INTRODUCTION

Hypertension represents the highest proportion of attributable mortality amongst all global risk factors and is a large burden to health care systems worldwide.(1, 52) There exists a strong, direct relationship between blood pressure and risk of stroke mortality, ischemic heart disease mortality, and all-cause mortality.(13)

Current guidelines recommend regular physical activity as a preventative measure and a first-line non-pharmacological treatment for hypertension.(20, 33, 53) Habitual leisure time physical activity has been shown to reduce all-cause mortality in both men and women.(54) A study of Harvard alumni showed that those who engaged in regular physical activity lived over a year longer than their sedentary counterparts.(23) Furthermore both leisure time physical activity and occupational activity have shown similar results with respect to reducing risk of death from ischemic heart disease.(24) A review of 44 papers concluded that the volume of physical activity and all-cause mortality are related in an inverse, linear dose-dependent manner.(55) Researchers have also shown that cardiorespiratory fitness, measured by maximal exercise stress testing, is related to mortality.(56) Of note, Blair and colleagues have shown that this is consistent for both normotensive and hypertensive men, in that men with higher cardiorespiratory fitness have a decreased risk of mortality.(42) Moreover, participation in aerobic(36, 57) or resistance(45, 46) exercise can lead to modest reductions in blood pressure.

Despite the available literature to support the benefits of physical activity on blood pressure and mortality in the general population, it is not clear whether these benefits translate to decreases in cardiovascular or all-cause mortality specifically in patients with

high blood pressure. Therefore, the purpose of this systematic review is to present the results of prospective longitudinal studies exploring the effect of physical activity on mortality (cardiovascular and all-cause) in patients with high blood pressure.

METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(58) The literature search was conducted using the Medline, Embase and Cochrane Library electronic databases and manual search from the reference list of relevant articles. Records were identified using standardized search terms. The Medline search strategy, as seen in Table 2.1, was adapted according to the respective indexing systems for the Embase and Cochrane Library databases. No previously established review protocol exists for this theme. English language longitudinal studies collecting data from human samples, published between the beginning of January 1985 and the end of January 2012 were considered, without any other limitations. The search and screening phases were conducted independently by two authors (AR and AD) with the help of two medical librarians; one from McGill University (AL) and the other one from Concordia University (DK). Any discrepancies were resolved through consensus. All the authors participated in the final selection of the included studies. Data was extracted by one author (AR) using an electronic form and checked for accuracy (AD). All authors have reviewed the extracted data. Variables of interest included: study and participant characteristics (e.g., length of follow-up, age, etc.), blood pressure and physical activity measurement tools and classification

schemes, method of mortality and cause of death verification, cardiovascular and all-cause mortality hazard ratios as well as study-specific covariates.

Retrieved records were retained if they fit all of the following criteria: (1) longitudinal design with a minimum 1 year follow-up; (2) adult participants (>18 years of age) had high blood pressure or hypertensive status was indicated; and (3) blood pressure, physical activity and cardiovascular or all-cause mortality were measured.

Risk of bias was evaluated in the selected studies using a modified version of the Downs and Black(59) tool so that only questions pertinent to prospective cohort studies were retained. This same method has been used previously.(60, 61) Thus 15 of the original 27 items (reporting: 1-4, 6, 7, 9, 10; external validity: 11-13; internal validity: 16-18, and 20) were considered for a possible total score of 15, where a higher score indicates better quality publication. Additionally, funnel plots were used to evaluate publication bias. In cases where group sample sizes were not detailed in the original article, efforts were made to contact the authors by telephone and email; however, identifying current contact information was not always possible.

A meta-analysis would have allowed us to quantify the overall effect of physical activity on mortality in this population. However, there was substantial a lack of consistency in the reporting of physical activity, whereby each study was classified in a different manner according to varying criteria in the self-report questionnaires, which made formal statistical analysis impractical. For instance, some studies classified physical activity groups according to the number of steps or city blocks walked each day, whereas other studies used minutes per day, metabolic equivalent scales or kilocalories per day to categorize participants.

RESULTS

A total of 3, 217 records were retrieved (see Figure 2.1). Of the 26 full-text articles(23, 39, 42, 43, 54, 56, 62-81) evaluated for eligibility, 20 were eliminated for the following reasons; in one article(65) the analysis was based on a sub-sample of a larger trial(73) included in the systematic review, two articles(42, 76) did not measure leisure time physical activity (only fitness or work activity were evaluated), and the remaining 17 studies(23, 54, 56, 62-64, 66-70, 74, 75, 77, 79-81) reported collecting data relating to blood pressure, physical activity, or mortality, but they did not evaluate the relationship between the three variables. Usually, physical activity and blood pressure were considered covariates in these reports. Thus, six studies were identified. Table 2 describes the characteristics of these studies. Altogether these studies evaluated 48, 448 men and 47, 625 women for a total of 96, 073 adults. Of the six studies, two considered only male participants (43, 71) and the remaining four included both men and women.(39, 72, 73, 78) Only three studies (39, 73, 78) reported results for men and women separately. The cohorts originated from Northern Europe (Denmark, Sweden, Iceland, Norway, Finland and the United Kingdom) or the United States of America. Medication usage was only indicated for the Losartan Intervention for Endpoint (LIFE) trial.(73) None of the other studies reported the type of medications, apart from stating that subjects using blood pressure lowering drugs were included and classified as hypertensive. Vatten et al.(39) stated that participants with specific co-morbidities were excluded, including patients using antihypertensive medications. Exclusions were also specified for the LIFE trial recruitment.(73) By design, the LIFE cohort also had left ventricular hypertrophy.(73) The National Health and

Nutrition Examination Survey I (NHANES I) report by Fang and colleagues (72) and LIFE trial, reported by Fossum et al.(73) were the only reports to include alcohol consumption and race/ethnicity; additionally NHANES I considered diet and socioeconomic measures in their model for analysis.

Amongst the articles selected are several sub-analyses of larger trials.(43, 72, 73, 78) In cases where information regarding the methods of blood pressure measurement, physical activity assessment, or mortality was not available in the text, the reference list or original publications were consulted.

Blood Pressure

Classification: According to the design of this review, each of the selected publications evaluated patients with high blood pressure; however, the criteria used to diagnose hypertension varied between studies. Engström et al.(71) used cut-off values of ≥160 mmHg or ≥95 mmHg for systolic and/or diastolic blood pressure, respectively, or self-reported use of anti-hypertensive medication. Fang et al.(72) and Hu et al.(78) established their own respective classification schemes (see Table 2.2). Fossum et al.(73) selected participants based on their blood pressure following 2 weeks of placebo treatment. If systolic blood pressure ranged between 160-200 mmHg and/or 95-115 mmHg they were classified as hypertensive and included in the cohort. In contrast, Vatten et al.(39) excluded subjects who reported using blood pressure lowering medications prior to entering the study. The authors established four categories for systolic (<120 mmHg, 120-139 mmHg, 140-159 mmHg, >160 mmHg) and diastolic (<80 mmHg, 80-89 mmHg, 90-99 mmHg,

≥100 mmHg) blood pressure classification spanning normotensive and hypertensive values. Paffenbarger et al.(43) stated that all participants were hypertensive, however they did not describe what blood pressure threshold level or criteria were used to define high blood pressure.

Measurement: Details for the measurement of blood pressure can be found in Table 2.3. Three studies(39, 71, 72) reported measuring blood pressure with a manual sphygmomanometer according to a defined protocol.(82) Engström et al.(71), Fossum et al.(73, 83, 84) and Fang et al.(72) specifically reported the patients to be in a seated position; however Paffenbarger et al.(43) and Vatten et al.(39) did not describe the posture of the participants. The LIFE trial reports indicate a standardized protocol was used to measure blood pressure.(83, 84) Hu et al.(78, 85) described all but one of their multiple sites to have measured blood pressure in the seated position; this single site evaluated patients in a recumbent position.(85) Although the method of blood pressure measurement was consistent within each participating site, the World Health Organization Multinational Monitoring of trends and determinants in **Ca**rdiovascular disease (MONICA) blood pressure assessment document(85) explained that both random-zero sphygmomanometers and simple sphygmomanometers were used. Details regarding measurement of blood pressure in the University of Pennsylvania College Alumni cohort(43) were not available.

Physical Activity Assessment

Classification: At baseline, the LIFE cohort(73) classified participants as sedentary (never active), intermediate (≤ 30 minutes of activity/week), or active (> 30 minutes/week) based on responses to their questionnaire. Engström et al.(71) conducted structured interviews and following an initial classification (almost completely inactive, some, regular and regular hard activity) they collapsed the groups into non-vigorous (i.e., inactive and some activity) and vigorous (i.e., regular and regular hard activity) groups. Fang et al.(72) asked their participants two questions regarding physical activity: "Do you get much exercise in things you do for recreation, or hardly any exercise, or in between?" and "In your usual day, aside from recreation, how active are you?" The MONICA cohort(78) qualified their occupational and leisure time physical activity as low, moderate, or high based on descriptors given for each respective type of physical activity. Additionally, commuting physical activity was classified as motorized, walk/cycle < 30 min or walk/cycle ≥ 30 min. Based on information collected about the number of city blocks walked per day, number of stairs climbed daily and the type and frequency of sport or recreational activities, Paffenbarger et al.(43) calculated a physical activity index which estimated the amount of kilocalories expended per week. However, for this analysis they only used a classification scheme according to level of sport participation. Vatten et al.(39) collected subjective information on the frequency of exercise, average duration of each session, activity intensity and based on responses graded participants into the following hierarchy: no activity, low, medium and high. Engström et al.(71) and Fang et al.(72) used

descriptive categories, whereas the remaining studies attempted to quantify physical activity by time(39, 73, 78) or by type and frequency of exercise.(39, 43)

Measurement: Information regarding physical activity was obtained through self-report in all studies. Engström et al.(71) conducted interviews with their participants, whereas all other studies reported using questionnaires.(39, 43, 72, 73, 78) General and leisure time physical activity were the main types of activity considered; however, Hu et al.(78) also collected information specifically relating to occupational and commuting physical activity (these results are not presented here). Each study established a classification scheme for activity levels (see Table 2.3).

Follow-up and Mortality

The length of follow-up ranged from almost 5 years up to 24 years. Cardiovascular mortality(39, 71-73, 78) and all-cause mortality(43, 71-73) were evaluated in the selected studies. Most studies obtained a confirmation of death through their respective national registries or official documentation.(39, 71, 72, 78, 86) No information was provided regarding how mortality data was acquired for Paffenbarger et al.(43)

The results from each study (all based on multivariate analyses) as well as the variables included in the respective statistical models are illustrated in Table 2.4. In hypertensive patients who engaged in vigorous physical activity (i.e., regularly active + regular hard activity), Engström et al.(71) found a significant lower risk of all-cause mortality (relative risk (RR)= 0.43, 95%CI: 0.22, 0.82) and cardiovascular mortality (RR= 0.33, 95%CI: 0.11, 0.94) when compared with hypertensive patients who did not engage in

vigorous physical activity. The same authors found that level of physical activity did not make a difference in mortality amongst normotensive participants.(71) Fang et al.(72) showed that patients with pre-hypertension who were active <30 minutes/day (HR= 0.79, 95%CI: 0.65, 0.97), but not those with higher levels of physical activity (HR=0.93, 95%CI: 0.74, 1.18), had a decreased risk of all-cause mortality. In hypertensive patients, active individuals had a 14-20% lower risk of cardiovascular death and similarly 12-17% lower all-cause mortality risk compared to their least active counterparts.

Overall, the active group from the LIFE(73) sample had a significant decrease in cardiovascular mortality compared to the sedentary group. A non-significant decrease of 20% was noted for those who participated in ≤30 minutes of activity/week. Compared to the sedentary groups, active men (HR=0.45, 95%CI: 0.33-0.61) and women (HR=0.55, 95%CI: 0.38-0.79) had a reduced risk of cardiovascular death. Men participating in ≤30 minutes/week of physical activity also had lower risk of cardiovascular mortality (HR=0.65, 95%CI: 0.47-0.90); however, there was no difference for moderately active women. Similar results were observed for all-cause mortality.

Hu et al.(78) demonstrated that hypertensive patients who engaged in moderate (some activity > 4 hrs/wk) or high (vigorous activity > 3 hrs/wk) levels of leisure time physical activity had a graded lower risk of cardiovascular death than those who engage in the lowest category of leisure time physical activity. Of note, similar results were observed in separate analyses for both sexes. Men and women who engaged in moderate activity had a 16% and 22% lower risk of cardiovascular mortality, respectively. Likewise, the most active groups showed further reductions in risk, totalling 27% and 26% decreased risk of cardiovascular death for men and women, respectively. The results from the University of

Pennsylvania College Alumni cohort indicated that hypertensive patients who engaged in combined light and vigorous sport participation had a 27% reduced risk of all-cause mortality.(43) Additionally, Paffenbarger et al.(43) found that the men who engaged in only vigorous sport participation displayed a 37% decrease in all-cause death. No decrease in mortality was observed with participation in only light activities.(43)

An extensive analysis by Vatten et al.(39) stratified risk across four categories of blood pressure and four levels of physical activity for both men and women, systolic and diastolic blood pressure alike, ultimately showed that regular physical activity was beneficial for patients with moderate hypertension in terms of lowering cardiovascular risk. Generally, the data displayed a pattern of increased risk with increasing blood pressure categories (systolic and diastolic) and decreasing levels of physical activity. The participants in the highest blood pressure group (systolic blood pressure >160 mmHg) who were inactive displayed greater than double the risk (men: RR 2.24, 95%CI 1.78, 2.83; women: RR 2.41, 95%CI 1.76, 3.30) of cardiovascular mortality compared to very active participants with lower blood pressure. Thus, all 6 studies have shown an inverse relationship between physical activity and cardiovascular or all-cause mortality.

Risk of Bias Assessment & Publication Bias

The results of this evaluation can be found in Table 2.2. Final scores ranged between 8 and 13 (mean ± standard deviation: 11.4 ± 1.9, median= 12). Four reports received high scores (≥12/15). Overall the studies rated well in the reporting category, with an average of 7/8 questions receiving full points. The studies received poor scores for

external validity (average 1 point out of 3). Information regarding the representativeness of the sample was generally unavailable. Additionally, whether or not the type of care provided was typical for the patients was not addressed. Three of the four questions assessing internal validity were given full points for each article. Where appropriate, most studies did indicate if analysis was adjusted for the length of follow-up. There was no discernable difference in reported outcome between the high- and low-scoring studies. Figure 2.2 is a funnel plot of sample size and log HR for all studies which provided individual group sample sizes(39, 71-73, 78). Generally, the sample sizes for each group varied (lowest n= 31, highest n= 7689). Overall there is no recognizable difference in symmetry for both cardiovascular and all-cause mortality, which suggests the absence of publication bias.

DISCUSSION

This systematic review examined the impact of physical activity on cardiovascular and all-cause mortality in patients with high blood pressure. An extensive literature search yielded 6 studies which addressed this question in prospective cohorts. Overall, the studies indicated that physical activity was inversely related with mortality in hypertensive patients, meaning patients with hypertension who were more active showed a lower cardiovascular (16-67% decrease) and all-cause (17-57% decrease) mortality. The results indicated that inactive men and women with high systolic blood pressure had more than double the risk of cardiovascular death.

Mechanisms

Physical activity has been shown to have an inverse relationship with blood pressure, as well as other cardiovascular disease risk factors and mortality in the general population.(23, 54, 87) Previous studies examining physical activity have demonstrated up to nearly 40% decreased risk of mortality in women and 35% decreased risk in men across all age groups.(54) The results of this systematic review also showed that this statement is true for patients with elevated blood pressure and/or hypertension. However, the mechanisms by which physical activity may exert this effect remain unclear. Meta-analyses have indicated that regular aerobic exercise(36, 57, 88) and resistance training(45, 46) decrease blood pressure between 2-6 mmHg. Similar modest decreases in blood pressure have been shown to decrease risk of cardiovascular events and cardiovascular mortality(89) by magnitudes comparable to those observed with physical activity in this review. Thus it is possible that the blood pressure lowering effect of regular physical activity and exercise can account for decreases in cardiovascular and all-cause mortality. Yet, the effects of physical activity on mortality may be concomitantly exerted through the reduction of other cardiovascular risk factors, e.g., improved glucose tolerance,(90) lower body mass index,(91) reduced platelet activity,(92) and reducing risk of co-morbid diseases, e.g., type 2 diabetes mellitus.(93) A review by Arakawa(35) highlighted changes in total peripheral resistance and a decrease in plasma volume and/or cardiac index as possible mechanisms, amongst several others, though there is not enough evidence available to draw strong conclusions. Fagard and colleagues(94) have also suggested a decrease in vascular resistance, driven by the sympathetic nervous system and renin-angiotensin systems, as the

main mechanism by which aerobic exercise reduces blood pressure. Patients with different types of hypertension, e.g. essential hypertension vs. preeclampsia, have an altered inflammatory profile.(95, 96) The sympathetic nervous system and renin-angiotensin system are impacted by anti-inflammatory (e.g. interleukin-6, IL-6) and pro-inflammatory (e.g. tumor necrosis factor-α, TNF-α) markers.(11) Moreover, IL-6 and TNF-α can affect endothelial cells and alter vascular function,(11) which is also implicated in the pathogenesis of hypertension.(97) Physical activity has been shown to improve endothelial function(98) even in clinical populations, for example, those with obesity,(99) coronary artery disease,(100) or exaggerated inflammation.(101) Thus these pathways may mediate the benefits of physical activity on blood pressure and mortality.

Other measures of arterial health, for example arterial stiffness which are inversely related to mortality(102) are also improved with exercise.(103) Improvements have also been observed in hypertensive patients after 4 weeks of aerobic exercise training.(104) Additionally, women who participate in regular physical activity are protected against the typical increases in arterial stiffness seen with aging.(105) Thus the benefits of physical activity in mediating the relationship between blood pressure and mortality are likely a result of changes in cardiovascular risk factors and overall arterial health. Nevertheless, evidence from the eligible reports suggests that physical activity can be employed for the primary prevention and management of hypertension and reducing risk of mortality.

Sex Differences

Amongst the six eligible studies, four included women in their sample populations and of those only three indicated risk for men and women separately.(39, 73, 78) The findings from all studies indicated that physical activity is protective for both men and women with elevated systolic or diastolic blood pressure. These benefits are similar in magnitude for both sexes, where highly active men gain between 27% and 45% reduced risk of cardiovascular mortality and women approximately 26%-55% reduced risk. Correspondingly, inactive men with elevated blood pressure have more than double the risk of cardiovascular mortality whereas the risk for women is almost two and a half times that of the active women with lower blood pressure. However, little to no consideration was given to potential differences between sexes in the remaining cohorts. Sex-related differences are especially important to consider given that the average age of participants ranged from 20-66 years old and blood pressure has been shown to differ between men and women across the lifespan.(106, 107) Through adulthood, women typically have lower blood pressure levels than men.(106, 107) However, during menopause and subsequently throughout the following decades, there is a shift in this trend, whereby the difference in incidence of hypertension between sexes narrows and is eventually higher in women.(106, 107) Additionally, age-adjusted comparison of the three phases of the NHANES survey has indicated that prevalence of hypertension tend to be higher in adult women compared to adult men.(108) Also, from 1988 to 2000 the change in prevalence increased in women to a greater extent than in adult men.(108) The mechanisms by which these shifts occur are not yet understood; however hormonal changes are thought to play a significant role.(106, 107)

Measurement of Physical Activity

The influence of the findings of these studies, or any other for that matter, rests in the quality of the measurement tools used to acquire relevant information. In this case, we are concerned with the quantification and classification of physical activity. Physical activity was consistently measured by self-report, whether through questionnaires or a structured interview.

Self-report is a poor measure of physical activity because the data collected is subject to 'recall bias' and can be dependent on the participants' health, mood, and depression amongst other psychological factors.(109) Despite being easy to administer, particularly when collecting data in large cohorts, these methods do not sufficiently capture vital information such as frequency, duration, intensity or volume of activity. Additionally, each of the studies had defined levels of activity based on the information available from their respective questionnaires, as opposed to standardized tools, which may not have been available at the time of data collection. Thus, what may be considered as a high level of activity according to one study, for example ≥ 30 minutes of activity per week,(65) does not equate with the definition of high activity in another report, e.g., vigorous activity > 3 hours/week.(78) These discrepancies make the direct comparison of results across studies virtually impossible and make it very difficult to identify the optimal frequency, duration, intensity, and volume of activity necessary to reduce the risk of death. Despite this shortcoming, the results still consistently indicate that there is a decrease in risk of mortality with increasing levels of activity, no matter how the latter are defined.

Another important aspect to consider when assessing physical activity in large cohorts is the age or age range of participants. Age is a determinant of activity energy expenditure and accordingly, older adults tend to spend most of their active time engaged in low intensity activities compared to younger age groups.(110) Measurement scales need to be sensitive enough to perceive these patterns. It has been shown that self-report tools validated to measure physical activity in younger adults are erroneous when used in older populations.(111) Thus, tools need to be customized specifically for the populations in question.

To overcome the fundamental flaws inherent in the use of self-report instruments, researchers are now recommending and standardizing the use of objective measures of physical activity, such as accelerometers.(112) These instruments allow for better characterization of the key physical activity parameters; frequency, duration, intensity, and volume(113) and if used consistently will allow for better comparison between studies. Additionally, accelerometers or similar devices can be worn throughout the waking day and over the course of several days, hence providing an excellent opportunity to capture not only leisure time physical activity, but commuting and occupational activity as well. Albeit, most of the data collected in the cohorts presented here pre-dates the advent of these new technologies; however moving forward, this should be taken into consideration.

Measurement of Blood Pressure and Hypertension

Another point of inconsistency between the studies was the definition of hypertension. Again, this is likely a result of the recruitment and/or follow-up periods pre-

dating standardized guidelines, which have since significantly evolved. However, this adds a level of confusion when comparing the results. For example, the individuals classified as hypertensive in the study by Engström et al.(71) (systolic blood pressure ≥160mmHg and diastolic ≥95mmHg) would instead be classified as having "moderate or severe" hypertension according to the scheme used by Hu et al.(78) As noted in the 2007 Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and European Society of Cardiology,(33) previous research has showed that the relationship between systolic and diastolic blood pressure and cardiovascular risk is linear only upwards of 110-115mmHg and 70-75 mmHg, respectively, thus creating a somewhat arbitrary cut-off point, designating anything above this point as hypertension. Risk of death from ischemic heart disease and stroke is linear upwards of these values and risk of death is increased two-fold for every increase in 20 mmHg for systolic blood pressure and 10 mmHg for diastolic blood pressure.(20) The grading of isolated systolic hypertension adds yet another level of complexity. Established guidelines vary according to the governing society and are continuously being revised, which has made and will continue to make room for confusion. Though there are differences between European(33), American,(20) and Canadian(53) guidelines it is important for researchers to follow recognized guidelines when classifying patients in order to establish some consistency across the literature.

The quality of blood pressure measurement, again likely subject to the era of data collection, was relatively sufficient across the studies, although not always described in the methods,(43, 72, 73, 78) and, ultimately, had to be obtained through other sources.(82, 83, 85) Blood pressure can vary depending on the time of day measured, the position of the

patient, and the type of equipment used(20), as such, it is important for these details to be specified. In the case of large cohort, multi-site trials it is important to standardize measurement techniques and ensure all operators have been properly trained to take accurate measurements using a standardized protocol. It may very well be that clear standardized protocols were followed in the measurement of blood pressure in the studies presented; however, the protocols were generally not well reported.

Limitations

Several limitations warrant consideration. Firstly, no meta-analysis was performed here due to the heterogeneity of the identified studies. Three of the six studies ranked low (< 12/15) in the risk of bias assessment. External and internal validity sections were generally rated with poor scores. Additionally, the reporting of general participant characteristics, such as age, height, weight, race/ethnicity, smoking status, alcohol consumption, and dietary factors, which are important with respect to the prevention and management of hypertension,(20) needs to be improved. Of the six studies selected only one, by Fossum et al.(73), described the pharmacological agents prescribed to the hypertensive participants. It is valuable for researchers to indicate medication usage so the readers are aware of the other treatments administered to these patients. This should be a standard component of reporting data for hypertensive subjects. The major limitations regarding quantification of physical activity, blood pressure classification, and sex differences have been discussed above. The main driving factor for this may be the period in which these data were collected, beginning as early as 1962.(43) However, moving

forward, this information should be considered necessary and methodological concerns should be addressed in future studies. Lastly, all of the selected studies are observational in nature and therefore any conclusions drawn herein do not infer causation. However, given that all of the results of these studies favour physical activity as beneficial for minimizing the risk of mortality related to high blood pressure, we consider this strong support for the role of exercise. To properly judge the causative role of physical activity in minimizing risk of mortality related to elevated blood pressure, randomized controlled trials would be required.

CONCLUSION

To the authors' knowledge, this is the first systematic review evaluating the impact of physical activity on mortality in individuals with high blood pressure. Following an exhaustive literature search, six articles were reviewed. Overall, the results indicate that there is an inverse relationship between physical activity and blood pressure in hypertensive patients. More research is warranted to determine the influence of activity frequency, duration, intensity and volume on mortality in participants with high blood pressure.

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FIGURES

Figure 2.1. Literature search results.

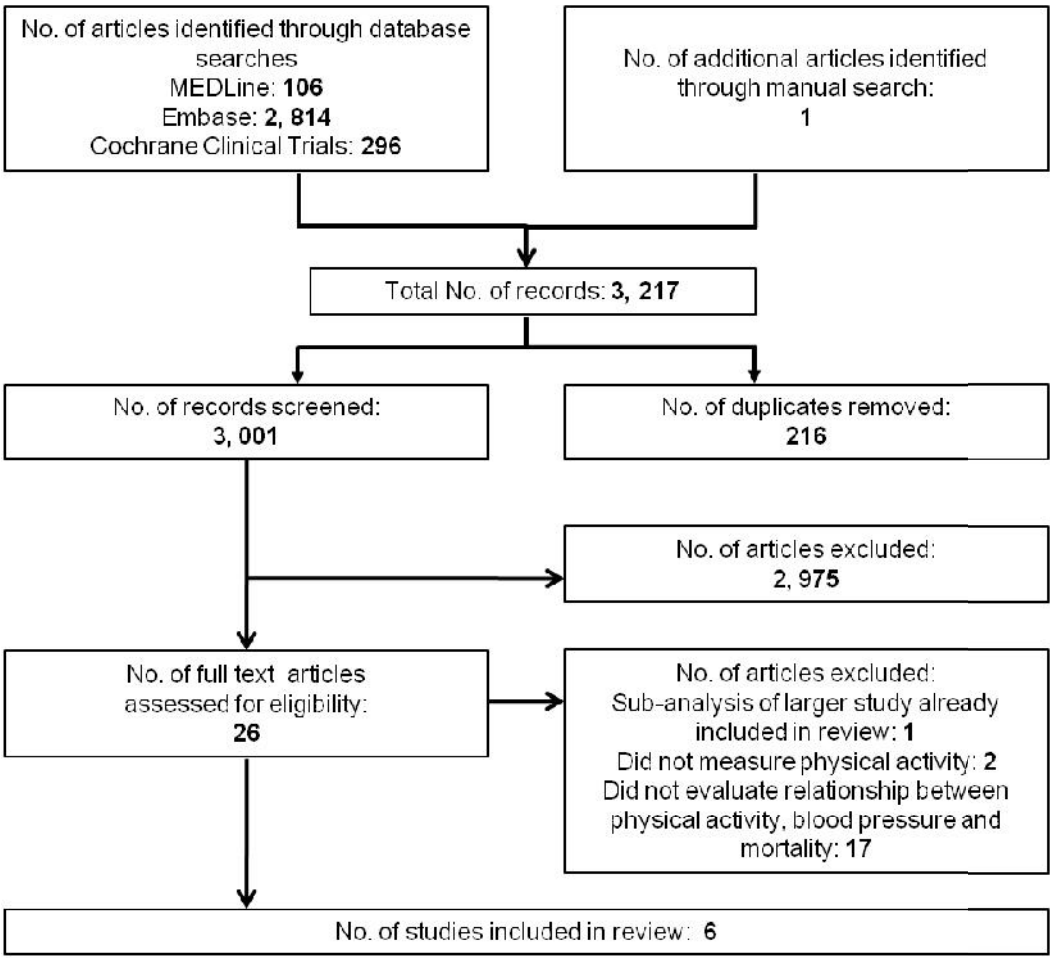
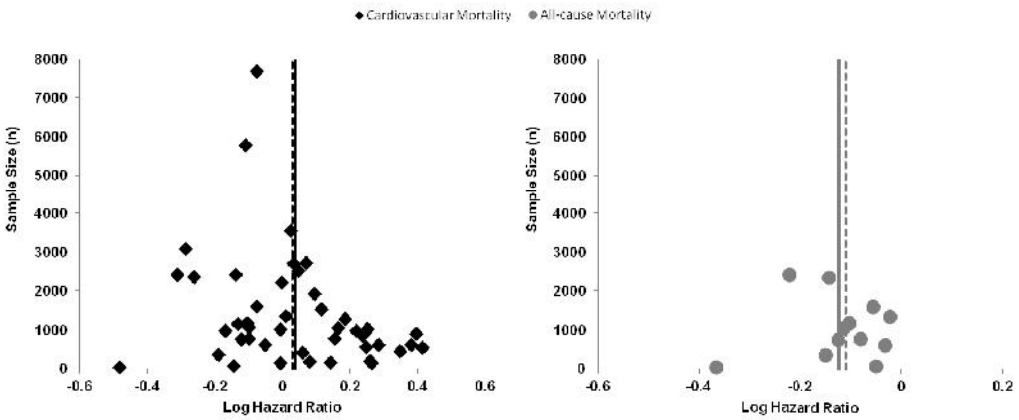


Figure 2.2. Funnel plots of sample size versus log HR in 46 groups for cardiovascular mortality (diamond markers, black lines) and 12 groups for all-cause mortality (round markers, grey lines). Solid vertical lines represent the mean log HR and dashed vertical lines indicate the median log HR.



TABLES

Table 2.1. Medline search strategy.

1. Hypertension/ or hypertens*.mp.
2. blood pressure.mp. or Blood Pressure/
3. Normotens*.mp.
4. Arterial pressure.mp.
5. 1 or 2 or 3 or 4
6. Exercise/ or exercise.mp.
7. physical active*.mp.
8. physical* active.mp.
9. Motor Activity/
10. resistance training.mp. or Resistance Training/
11. exercise*.mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. Mortality/
14. Death/
15. Fatal Outcome/
16. 13 or 14 or 15
17. 5 and 12 and 16
18. Limit 17 to (English language and humans and yr="1985-Current")

Table 2.2. Study and sample characteristics.

First Author (Year)	Country	Study	Follow-Up (years)	N	Sex (female/male)	Baseline Age (years)	BMI (kg/m^2)	Co-morbid Conditions[†]	Meds[‡]	D&B Score
Engström (1999)(71)	Sweden	-	23.8 (1968/69-death/December 1993)	642	0/642	55	24.5-24.5	No CVD	No	11
Fang (2005)(72)	U.S.A	National Health and Nutrition Examination Survey (NHANES I)	11.8-17 (1971/1975- June 1992)	9791	6011/3780	38-55	22.8-27.04	No exclusions indicated	No	12
Fossum (2007)(73)	Denmark, Finland, Iceland, Norway, Sweden, United Kingdom, U.S.A	Losartan Intervention for Endpoint (LIFE)	4.8	9185	4961/4224	66-67	27.4-29.1	Left Ventricular Hypertrophy	Yes	10
Hu (2007)(78)	Finland	-	6.6-31.7; mean: 19.9 (1972-2003)	26643	12244/14399	41-51	26.1-28.6	No exclusions indicated	No	13
Paffenbarger (1991)(43)	U.S.A	College Alumni Health Study, University of Pennsylvania Cohort II	24 (1962-1985)	819	0/819	-	-	No exclusions indicated	No	8
Vatten (2006)(39)	Norway	Nord Trøndelag Health Study (HUNT)	16 (1984/86-death/December 2002)	48993	24409/24584	≥ 20	-	Excluded participants	No	13

†Indicates if patients with comorbid diseases were included in the study. ‡Indicates whether or not the participants' medication use was reported. BMI: body mass index, CVD: cardiovascular disease, Meds: medications, D&B: Downs and Black(59).

Table 2.3. Summary of methods and classification schemes for selected studies.

First Author (Year)	Blood Pressure		Physical Activity		Mortality & Cause of Death
	Classification	**Measurement**	**Classification**	**Measurement**	
Engström (1999)(71)	*Hypertension* SBP ≥ 160 mmHg or DBP ≥ 95 mmHg or reported using antihypertensive medication	Morning, seated position, measured to nearest 5mmHg with mercury sphygmomanometer and 12x16 rubber cuff	*Non-Vigorous:* Inactive(group 1) + Some activity (group 2) *Vigorous:* Regularly active (group 3) + Regular Hard activity (group 4)	Structured interview	Mortality Register, Swedish National Bureau of Statistics; ICD, 8th & 9th revision
Fang (2005)(72)	*Normal BP* no history of hypertension and BP <120/80 mmHg *Pre-hypertension* no history of hypertension & BP 120-139/80-89 mmHg *Hypertension* history of hypertension, reported using antihypertensive medication, BP ≥140/90 mmHg	Seated position, with weekly calibrated manometer & falling pressure at 2-3mmHg, measured to nearest 2mmHg(82)	*Recreational activity* 1. low activity 2. moderate activity 3. high activity	Self-report questionnaire; Only considered "recreational activity"	Death certificate or proxy respondent; ICD, 9th revision

Fossum (2007)(73)	*Hypertension* SBP 160-200 mmHg and/or DBP 95-115 mmHg after 2 weeks of placebo treatment	Seated position following a standardized protocol(83, 84)	*Sedentary*: never active *Intermediate*: ≤ 30min/wk *Active*: > 30 min/wk	Self-report questionnaire	Deaths were reported separately and directly to the independent data and safety monitoring board for validation(86)
Hu (2007)(78)	*Hypertension* SBP ≥140 OR DBP ≥90, using or approved reimbursement for antihypertensive medication *Moderate or Severe Hypertension* SBP ≥160 or DBP ≥95	Varied across sites (mainly seated position), simple or random-zero sphygmomanometer(85)	*Low*: almost completely inactive *Moderate*: some physical activity >4 hrs/wk *High*: vigorous activity >3 hrs/week	Self-report questionnaire; Leisure time physical activity	Statistics Finland; ICD, 8th, 9th, & 10th revision
Paffenbarger (1991)(43)	-	-	*Sport Participation* none, light only, light & vigorous, vigorous only	Self-report questionnaire; Only sport participation	-
Vatten (2006)(39)	*Blood pressure groups* SBP: <120, 120-139, 140-159, ≥160 mmHg DBP: <80, 80-89, 90-99, ≥100 mmHg	Calibrated mercury manometers, standard cuff size, measured to the nearest 2mmHg	1. no activity & three equal activity groups; 2. low, 3. medium, & 4. high	Self-report questionnaire	Cause of Death Registry, Norway

SBP: systolic blood pressure, DBP: diastolic blood pressure, ICD: International Classification of Diseases

Table 2.4. Summary of cardiovascular and all-cause mortality results for selected studies.

First Author (Year)	Cardiovascular Mortality	All Cause Mortality	Multivariate Model*
Engström(71) (1999)	*Relative Risk (95% CI)* Hypertensive/Vigorous physical activity: 0.33(0.11-0.94) Hypertensive/Non-vigorous physical activity: 1.00 Normotensive/Vigorous physical activity: 0.72(0.39-1.35) Normotensive/Non-vigorous physical activity: 1.00	*Relative Risk (95% CI)* Hypertensive/Vigorous physical activity: 0.43(0.22-0.82) Hypertensive/Non-vigorous physical activity: 1.00 Normotensive/Vigorous physical activity: 0.89(0.60-1.31) Normotensive/Non-vigorous physical activity: 1.00	Normotensive: smoking; Hypertensive: smoking, antihypertensive therapy & SBP
Fang(72) (2005)	*Hazard Ratios (95% CI)* Normotensive: LPA 1, MPA 0.76 (0.39–1.49), HPA 0.65 (0.24–1.77) Prehypertensive: LPA 1, MPA 0.79 (0.58–1.09), HPA 0.89 (0.61–1.31) Hypertensive: LPA 1, MPA 0.84 (0.73–0.97), 0.80 (0.66–0.96)	*Hazard Ratios (95% CI)* Normotensive: LPA 1, MPA 0.75(0.53–1.05), HPA 0.71 (0.45–1.12) Prehypertensive: LPA 1, MPA 0.79 (0.65–0.97), HPA 0.93 (0.74–1.18) Hypertensive: LPA 1, MPA 0.88 (0.80–0.98), HPA 0.83 (0.72–0.95)	Age, gender, race, BMI, education, diabetes, smoking, alcohol, dietary caloric, sodium, calcium & potassium intake, SBP & serum cholesterol
Fossum(73) (2007)	*Hazard Ratios (95% CI)* Sedentary: reference, Intermediate: 0.80 (0.63-1.01), Active: 0.49 (0.39-0.62)	*Hazard Ratios (95% CI)* Sedentary: reference, Intermediate: 0.85(0.71-1.02), Active: 0.65(0.55-0.77)	Baseline current smoking, alcohol, gender, age, race,

	Men Sedentary: reference, Intermediate: 0.65 (0.47-0.90), Active: 0.45 (0.33-0.61) Women Sedentary: reference, Intermediate: 1.029 (0.73-1.44), Active: 0.55 (0.38-0.79)	Men Sedentary: reference, Intermediate: 0.77 (0.60-1.00), Active: 0.60 (0.48-0.76) Women Sedentary: reference, Intermediate: 0.95 (0.74-1.24), Active: 0.72 (0.56-0.92)	left ventricular hypertrophy, Framingham risk score.†
Hu(78) (2007)	*Hazard Ratios (95% CI)* Men: Low 1, Mod 0.84 (0.77–0.91), High 0.73 (0.62–0.86); trend p<.001 Women: Low 1, Mod 0.78 (0.70–0.87), High 0.74 (0.58–0.94); trend p<.001	-	Age, study year, education, alcohol, smoking, BMI, SBP, cholesterol, antihypertensive drug use & diabetes
Paffenbarger(43) (1991)	-	*Relative Risk* None 1.00, Light only 1.00 Light and vigorous 0.73, Vigorous only 0.63, trend p=0.1276	Adjusted for age

Vatten(39) (2006) †	*Relative Risk (95% CI): high, medium, low, no activity* Men <120 mmHg: 0.68(0.43–1.07), 0.99(0.70–1.39), 0.78(0.51–1.20), 1.15(0.72–1.85) 120-139 mmHg: 1.00(Reference), 1.06(0.86–1.32), 0.99(0.78–1.26), 1.31(1.02–1.67) 140-159 mmHg: 1.21(0.97–1.52), 1.25(1.02–1.55), 1.39(1.11–1.74), 1.73 (1.37–2.19) >160 mmHg: 1.82(1.46–2.28), 1.76(1.42–2.17), 1.84(1.45–2.34), 2.24 (1.78–2.83) Women <120 mmHg: 0.52(0.28–0.97), 1.00(0.61–1.65), 1.08(0.62–1.86), 1.43 (1.84–2.44) 120-139 mmHg: 1.00(Reference), 1.12(0.80–1.57), 1.18(0.81–1.73), 1.79(1.26–2.53) 140-159 mmHg: 1.47(1.04–2.09), 1.54(1.12–2.12), 1.66(1.17–2.34), 1.93 (1.39–2.69) >160 mmHg: 1.77(1.26–2.54), 2.49(1.84–3.37), 2.60(1.87–3.60), 2.41 (1.76–3.30)	-	Age, BMI, marital status, education, alcohol & smoking

Data presented herein are results from multivariate analyses for all studies; unadjusted results are not shown in this table. †Only results for systolic blood pressure are presented here; a similar pattern for diastolic blood pressure was observed(39). LPA: low physical activity, MPA: moderate physical activity, HPA: high physical activity, SBP: systolic blood pressure, BMI: body mass index.

SUPPLEMENTAL MATERIALS: SYSTEMATIC REVIEW UPDATE

Below is an update to the systematic review presented herein which was published in 2012.(114)

METHODS

Using the same strategy previously described in Chapter 2, the searches were repeated in the same databases from January 2012 (i.e., the cut-off of the previous search) until June 2015. A total of 1,713 unique records were retrieved (see Figure 2S.1). Three publications were selected for full-text review. Of these, only one was deemed eligible.(115)

RESULTS

The study by Brown et al.(115) is a very interesting addition to this group of literature. The authors elaborate on previous work by further categorizing participants according to whether their blood pressure was uncontrolled (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure > 90 mmHg) or controlled (<140/90 mmHg), and whether they were treated with antihypertensive medication (treated) or not (untreated). Physical activity was classified as active (participating in one or more bouts of at least moderate activity per week) or inactivity (participating in no weekly physical activity). Of note, the authors only considered leisure time physical activity.

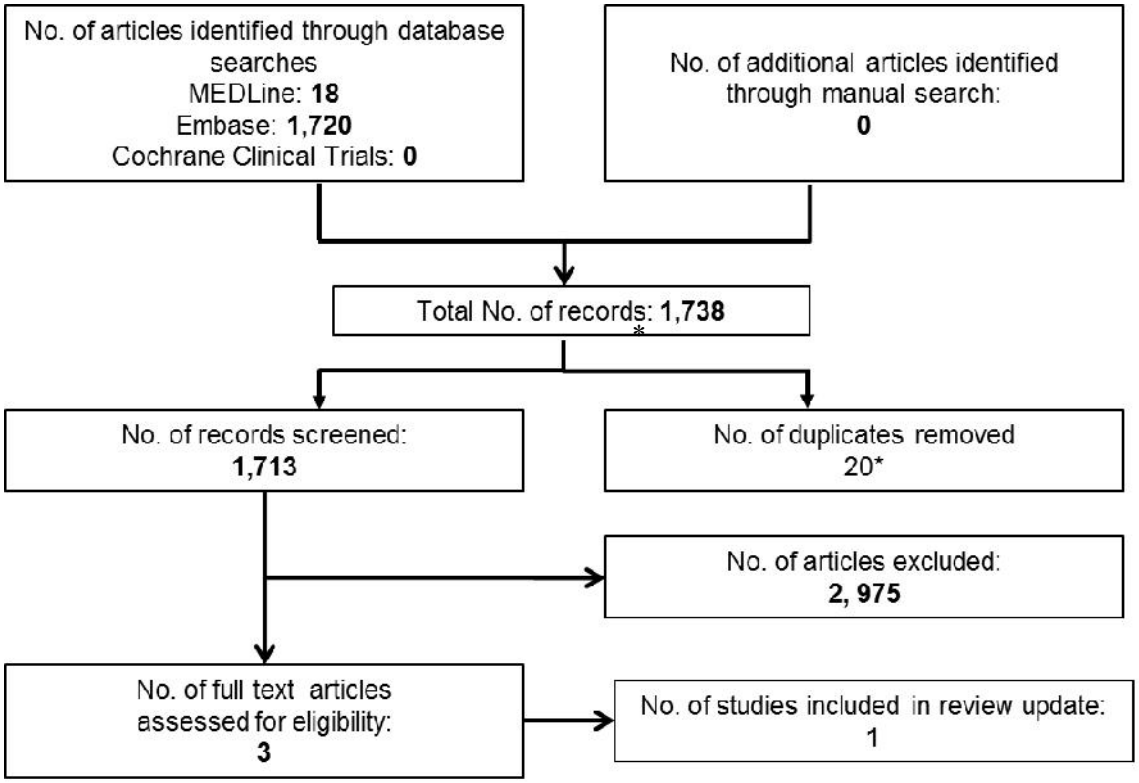
There were no interactions observed for physical activity, pharmacological anti-hypertensive treatment, and blood pressure control. The results of their study showed that being physically active reduced the risk of mortality (see Table 2S.3). Having controlled blood pressure also significantly reduced the risk of death; however being on pharmacological anti-

hypertensive treatment was indicative of an increased risk of mortality. The results also showed that compared to the active hypertensive treated and controlled (i.e., the target for hypertension) referent group, the inactive participants in all the hypertensive groups (i.e., 1) treated and controlled; 2) treated and uncontrolled; and 3) untreated and uncontrolled) all had a significantly higher risk of mortality. Conversely, the normotensive active group had a lower risk of mortality compared to the active hypertensive treated and controlled group. No significant difference was noted for the inactive normotensive group compared to the referent group. Thus, the authors conclude that their findings imply that physical activity was equally important, if not more so, than anti-hypertensive treatment for decreasing risk of mortality in patients with hypertension, and that prevention of hypertension was vital.

CONCLUSIONS

These findings are a very unique addition to the systematic review because of the consideration given to pharmacological anti-hypertensive medication usage and whether or not blood pressure was controlled. However, certain methodological concerns with regards to physical activity classification still persist. The authors used a minimum of one bout of at least moderate intensity physical activity per week as their cut-off to define active vs. inactive. Whilst this further supports the idea that "any physical activity is better than none," it is difficult to place these results relative to current guideline recommendations.

Figure 2S.1. Literature search results.



* Includes duplicates which overlapped with articles previously retrieved in January 2012.

Table 2S.1. Study and sample characteristics.

First Author (Year)	Country	Study	Follow-Up (years)	N	Sex (female/male)	Baseline Age (years)	BMI (kg/m^2)	Co-morbid Conditions[†]	Meds[‡]	D&B Score
Brown (2013)	USA	NHANES III	8.6	10,665	5540/5125	64.5	26.6-28.9	No exclusions	Yes	10

Table 2S.2. Summary of methods and classification schemes for selected studies.

First Author (Year)	Blood Pressure		Physical Activity		Mortality & Cause of Death
	Classification	Measurement	Classification	Measurement	
Brown (2013)	Self-reported physician diagnosis of hypertension, or taking antihypertensive medications, or SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	Mercury sphygmomanometer according to standardized protocol; average of six readings; (3 sets of measurements taken by trained professional)	*Active:* one or more bouts of at least moderate activity per week *Inactive:* no weekly physical activity.	Questionnaire	U.S. National Center for Health Statistics, National Death Index

Table 2S.3. Summary of cardiovascular and all-cause mortality results for selected studies.

First Author (Year)	All-Cause Mortality	Multivariate Model*
Brown (2013)	Hazard Ratios (95%CI) Physically active: HR, 0.71; 95% CI, 0.66–0.78; *P* < 0.001 Controlled BP: HR, 0.84; 95% CI, 0.78–0.92; *P* = 0.004 Treated: HR = 1.29, 1.18–1.40; *P* < 0.001 Individual Hazard Ratios for each group were not reported, only shown in graphical format (see Brown et al. 2013; Figure 2)	age, sex, education, ethnicity, smoking status, Type 2 Diabetes, dyslipidemia, CVD, and body mass idex

CHAPTER 3 | THE ASSOCIATION OF BLOOD PRESSURE AND PHYSICAL ACTIVITY ON CARDIOVASCULAR AND ALL-CAUSE MORTALITY: THE SCOTTISH HEALTH SURVEY

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Preamble

The findings of the systematic review indicate that there was an inverse relationship between physical activity and mortality in individuals with high blood pressure. In order to better understand precisely how the two factors (physical activity and blood pressure) act together to reduce risk of mortality and CVD, we proposed to build an interaction model. Also, we specifically sought to improve on shortcomings identified in the systematic review; e.g., examining physical activity volume and including CVD events in our main outcome

ABSTRACT

Objective: the purpose of this study was to specifically examine the main and interaction effects of different levels of physical activity and blood pressure on both fatal and non-fatal cardiovascular (CVD) events, and mortality. **Methods**: Data from the Scottish Health Survey participants recruited in 1995, 1998, and 2003 (8747 participants; age: 53.5 years, 57% women) was analyzed. Physical activity was assessed via questionnaire and classified as <1 bout per week, 1-4 bouts per week, or 5+ bouts per week of at least 30 minute bouts of physical activity. Repeated resting blood pressure measurements were taken. Follow-up was censored to December 2007. Hospitalization and cardiovascular disease history was acquired through patient-based database. Cox proportional hazards models (with interaction term) were used to calculate the risks of incident cardiovascular disease (fatal and non-fatal events combined) and all-cause mortality. **Results**: We found main effects of blood pressure (systolic, p <0.001; diastolic, p <0.01); however no significant main effect of physical activity was observed for CVD. There was a significant interaction between systolic blood pressure and physical activity (p= 0.014) such that doing any level of activity for the blood pressure groups < 160 mmHg reduced risk of CVD; in those with systolic blood pressure ≥ 160 mmHg, there was no change in risk. A main effect of systolic blood pressure was found for mortality (p= 0.01) No main effects for diastolic blood pressure or physical activity were noted, nor was there a significant interaction. **Conclusions**: The results showed that physical activity and blood pressure do not interact together to influence mortality. However, do interact to impact CVD development, showing benefits of physical activity for individuals with systolic blood pressure < 160 mmHg. The findings suggest that physical activity may impact mortality indirectly through blood pressure.

INTRODUCTION

Hypertension is one of the leading risk factors for the development of cardiovascular disease (CVD) and CVD death with a strong, direct relationship between increasing blood pressure and risk of all-cause mortality, stroke mortality and ischemic heart disease mortality.(13)

A recent systematic review explored the relationship between physical activity, blood pressure and (cardiovascular and/or all-cause) mortality.(114) Some of the studies included in this review considered, for example, the effect of physical activity on mortality in only hypertensive participants,(43, 73, 78) others compared risk of all-cause or cardiovascular mortality between groupings of combined physical activity status and hypertension status.(71, 72) For example, Engtröm et al.(71) evaluated risk of cardiovascular and all-cause mortality by classifying participants by both hypertension status (normotensive vs. hypertensive) and physical activity (vigorous vs. non-vigorous), resulting in 4 groups and using one group as the referent. Along the same lines, Vatten et al.(39) combined four categories of blood pressure and four levels of physical activity; thus creating 16 groups and using one group (example, systolic blood pressure= 120-139 mmHg with high physical activity) as the referent to determine risk of cardiovascular death.(39) Whilst the results consistently showed that regular physical activity was beneficial for reducing mortality in patients with high blood pressure,(114) we lack a more statistically nuanced understanding of how physical activity and blood pressure act together to effect cardiovascular outcomes and death. Additionally, none of the studies have measured CVD events, they have only measured risk of CVD death. Given that the risk of recurrence of cardiovascular events following a first event remains high,(116) it is important to also consider these non-fatal events as an outcome.

Thus, the purpose of this study was to specifically examine the main and interaction effects of different levels of physical activity and blood pressure on both fatal and non-fatal cardiovascular events, and mortality.

METHODS

Study Population

Information regarding sample design and selection has been published previously.(117, 118) The population-based Scottish Health Survey (SHS) was conducted in individuals living in households from the general population in Scotland. Different samples were surveyed in 1995, 1998 and 2003. SHS samples were selected using multi-stage stratified probability design to give a representative sample of the target population. Stratification was based on geographical entities and not on individual characteristics: postcode sectors selected at the first stage and household addresses selected at the second stage. Each participant was visited twice in their homes; firstly by an interviewer and secondly by a nurse. The overall response rate (interviewer home visit) ranged between 60-90 % for different survey years, with 33-41 % of all eligible participants seeing a nurse during a subsequent home visit. All participants gave informed consent. Ethical approval was obtained from the Local Research Ethics Councils and all procedures conform with the Declaration of Helsinki.

Physical Activity

Physical activity was measured by questionnaire.(118) The 1998 and 2003 physical activity self-report questionnaire asked respondents to report both frequency (days in the last 4 weeks) and duration (number of minutes per day) of participation in the following activities; heavy housework (*e.g.*, scrubbing floors, cleaning windows), heavy ‘‘do-it-yourself’’ activities/gardening (*e.g.*, sweeping leaves, digging, building work), walking for any purpose, and any leisure-time sports/exercises (*e.g.*, cycling, swimming, gym, dancing, football or rugby, racket sports). The 1995 version of the physical activity questionnaire also included duration and frequency throughout an average week with the same domains as the 1998 and 2003 questionnaires. Duration and frequency, however, were described as categorical variables (frequency: 5 point scale ranging from zero participation to 6-7 times/week; duration: no time to 2 hours or longer). The 1995 data was converted to continuous variables by taking the midpoint of each category. For example, ‘‘2–3 times a week’’ was set to 2.5 times, and‘‘20 minutes, less than 30 minutes’’ was set to 25 minutes in order to be harmonized with the more recent data sets and all data were converted to weekly averages.(118) The criterion validity of these questions is supported by the results of a recent study on 106 British adults from the general population (45 men) where the output of accelerometers (worn for two non-consecutive weeks over a month period) was compared against the questionnaire output. The questionnaire appeared to be a valid measure of moderate to vigorous physical activity (sessions/week), intra-class correlation coefficients were 0.47 in men (P=0.03) and 0.43 in women (P=0.02).(119) Participants were divided into three groups according to their frequency of participation in minimum 30 minute bouts of physical activity; less than 1 bout, 1-4 bouts, or 5 or more bouts per week.

Blood Pressure

Three automated blood pressure measurements (Omron HEM-907 blood pressure monitor) were taken in a seated position by a trained individual.(120) The correct cuff size was determined for each individual. The mean of the 2nd and 3rd readings was used for the analyses reported here. To define hypertension we used measured blood pressure ≥140/90 mmHg and/or anti-hypertensive medication usage.

Mortality

Follow-up data was collected from entry into the study and censored to December 2007. Information regarding events and hospitalization with a diagnosis of CVD as early as 1980 and deaths were acquired through linkage to a patient-based database.

Deaths were classified according to the International Classification of Diseases, 9th Revision (CVD codes 390-459) and 10th Revision (CVD code I01-I99). In order to limit reverse causation, participants were excluded from the analysis if they had previously experienced a nonfatal cardiovascular event or had previously diagnosed CVD.

Statistical Analysis

The primary outcomes of interest were 1. incident CVD (combined fatal and non-fatal events incorporating acute myocardial infarction, coronary artery bypass surgery, percutaneous coronary angioplasty, stroke, and heart failure) and 2. all-cause mortality. Blood pressure was divided into four categories; systolic blood pressure < 120 mmHg, 120-139 mmHg, 140-159

mmHg, ≥ 160 mmHg, and diastolic blood pressure < 80 mmHg, 80-89 mmHg, 90-99 mmHg, ≥ 100 mmHg, with both systolic and diastolic blood pressure analysed in separate models. Cox proportional hazard models were used to calculate risk of CVD incidence (fatal and non-fatal events combined) and all-cause mortality. We first analysed the main effects of blood pressure (systolic and diastolic) and physical activity on incident CVD and mortality. The analyses were subsequently repeated using an interaction term within our Cox proportional hazard model. Covariates included age and sex for Model 1, and age, sex, smoking status (never smoked, former smoker, current smoker), family history of hypertension (yes/no), social class (Registrar General classification I/II, III non-manual, III manual, IV/V), and CVD medication usage (blood pressure- lowering, and lipid-lowering, including statins)for Model 2. Secondary analyses examining hypertension status and physical activity were also conducted using the same set of covariates as defined above. All analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

Participant characteristics

A total of 16,144 participants were included in the surveys, although 3,036 participants (18.8%) did not consent to follow up and were removed from the analyses. The 884 subjects (5.2%) who reported a history of cardiovascular disease or who experienced an event within the first 12 months of follow up were also excluded. Additionally, 3,477 participants (21.5%) were excluded as a result of missing data mainly due to participants who did not consent to the nurse's visit. Thus a total of 8,747 participants (age: 53.5 years, 57% women) were included in this

analysis. The participant characteristics are displayed in Table 3.1. Over a mean follow period of 7.1 years there were 851 deaths, 30.3% of which were cardiovascular disease, and 995 (11.4%) of the participants had at least 1 CVD event.

CVD: Main & Interaction Effects

The results showed a significant main effect for physical activity, such that the most active participants (i.e., ≥ 5 bouts/week) had the lowest rate of CVD incidence in the systolic ($p < 0.01$) and diastolic ($p < 0.01$) blood pressure models. Main effects of systolic (<0.0001) and diastolic (<0.001) blood pressure were also significant (Model 1). With the additional covariates (Model 2), main effects of blood pressure were maintained (systolic, $p < 0.001$; diastolic, $p < 0.01$); however physical activity was no longer significant. Hazard ratios (HR) and 95% confidence intervals (95%CI) for the main effects of physical activity and blood pressure models are presented in Tables 3.2 and 3.3 (systolic and diastolic, respectively).

The interaction model showed a significant interaction between physical activity and systolic blood pressure ($p = 0.033$). The interaction maintained significance in Model 2 ($p = 0.014$). Figure 3.1 shows the Hazard Ratios for the interaction between physical activity and systolic blood pressure (see discussion for a description of the interaction). There was no interaction between physical activity and diastolic blood pressure for Model 1 or 2.

All-cause Mortality: Main & Interaction Effects

The Hazard Ratios and 95%CIs for the main effects of systolic and diastolic blood pressure and physical activity on all-cause mortality can be found in Table 3.4 and 3.5, respectively. The results (Model 1) indicate a main effect of systolic blood pressure ($p = 0.01$) and physical activity ($p = 0.004$); however, physical activity did not maintain significance in Model 2 ($p = 0.055$). Significant main effects of diastolic blood pressure ($p = 0.043$) and physical activity ($p = 0.003$) were observed for all-cause mortality for Model 1. No significant main effects were found in Model 2. No significant interactions were observed between systolic blood pressure and physical activity, nor between diastolic blood pressure and physical activity (both Models 1 & 2). See Figure 3S1. in the Supplemental Materials.

Hypertension Status

Hypertension status showed a significant main effect on CVD ($p<0.0001$) such that being hypertensive increased the risk of CVD (HR: 1.84, 95%CI: 1.54, 2.02) (Model 2). There was no significant main effect of physical activity and no interaction observed. No significant main or interaction findings were observed for all-cause mortality. See Figures 3S.2 and 3S.3 in the Supplemental Materials.

DISCUSSION

The findings of our study show similar results as previous reports in terms of the main effects for blood pressure and physical activity on CVD and mortality.(114) However, this is the

first paper to explore both of these outcomes using an interaction term between the two variables. The inclusion of non-fatal CVD events is an important addition to the analyses because prior events are a significant source of morbidity leading to increased risk of all-cause mortality, reduced quality of life, and increased health care costs.(121-123)

We found an interaction effect of physical activity and blood pressure for major CVD events, but not for mortality. As seen in Figure 1, <1 bout of physical activity per week increases risk of CVD events in individuals with systolic blood pressures of 120-139 mmHg (prehypertension) and 140-159 mmHg (stage 1 hypertension), with no difference between those who do 1-4 or ≥5 bouts per week. Thus, the data may indicate that for these blood pressure groups, any level of physical activity is beneficial for preserving cardiovascular health. In the grouping of participants with systolic blood pressure > 160 mmHg (stage 2 hypertension), there was no change in risk across physical activity levels. Thus, physical activity of any volume does not benefit these hypertensive participants indicating that aggressive pharmacotherapy or multiple health behaviour changes in this group may be needed to reduce the risk of CVD events. We also observe an unexpected pattern of risk for the participants with systolic blood pressure <120 mmHg. Compared to the most active group, the data show an increased risk of CVD events for those who do not meet optimal physical activity levels (i.e., 1-4 bouts/week), which is consistent with previous literature,(124-126) and no change in risk in the lowest physical activity group, which is inconsistent with the previous literature. Though there does not seem to be a clear explanation for the lack of a difference in the CVD event risk between those normotensive participants doing the highest and the lowest levels of physical activity, we can speculate as to why we saw this. The lack of difference suggested there was perhaps some protective characteristic attributed to this group. Based on the literature reporting that blood pressure

increases with age,(127) and the idea that perhaps age would be protective (i.e., negating the potential harms of inactivity, younger individuals might not yet present with high blood pressure), we explored whether there were age differences across the groups. However, the analyses did not show an age difference, indicating that this could not account for the finding. It is possible that the finding was spurious, and it would be important to see if this was replicable in other similar studies. If this is the case then a potential mechanism would need to be explored.

The lack of interaction between physical activity and all-cause mortality, however, may indicate that the effects of physical activity on overall longevity seen in other studies are likely moderated by other variables. For example, physical activity has been associated with healthy weight management, improved mental and vascular health markers, and quality of life.(100, 128-130) In addition, evidence suggests that physical activity directly impacts vascular wall function, therefore improving cardiovascular risk beyond traditional risk factor modification.(131) Visual inspection of Figure S1, suggests that in those patients with systolic blood pressures up to 160 mHg, there are improvements in mortality risk in those do some activity (≥1 bouts per week) compared to those doing no discernible activity (< 1 bout per week). It may be that reducing sedentary behaviours, which has been shown to increase the risk of incident hypertension and impaired vascular function independent of physical activity,(132, 133) may be more impactful that increasing physical activity in these groups. However, given that this is a non-significant finding and we did not actually measure sedentary behaviours these need to be assessed appropriately in future studies.

Limitations

Our study has several limitations. Data on physical activity was acquired through self-report questionnaire which could be a source of bias.(109) However, the measures were validated with accelerometry.(119) Underlying disease may have introduced potential bias into our analyses, because participants with poorer health might have been less likely to participate in more vigorous activities. However, we took robust measures to address reverse causation by removing any participants with clinically confirmed CVD at baseline and participants who had experienced any events in the first year of follow-up, and making statistical adjustment for indicators of underlying disease such as use of CVD medication. Lastly, another limitation was that we did not take into account diet or salt intake, which are important factors to consider with respect to blood pressure. We did not perform additional multi-variable adjustments for other clinical risk markers such as body mass index, cholesterol, and inflammatory markers, since these might be mechanisms on the causal pathway explaining the cardio-protective effects of physical activity.(118) Finally, despite reinforcing what we have previously seen, our results from a large, contemporary sample also raise questions about the strength of the associations and type of relationship (e.g., moderation, mediation, causality) between physical activity, blood pressure, and CVD and mortality. It is prudent to note that despite the added support for associations, and inference of moderation and assumptions of causality cannot be made from these observational data. As such, future research is needed to address the limitations of the current literature.

CONCLUSIONS

Whilst there is strong evidence of a relationship between physical activity and blood pressure, the observations from the present study suggest the two do not interact together to influence mortality, and may interact to impact CVD development, despite showing main effects for each variable. Further research is warranted to determine the exact mechanisms by which blood pressure and physical activity may exert CVD and mortality-reducing effects.

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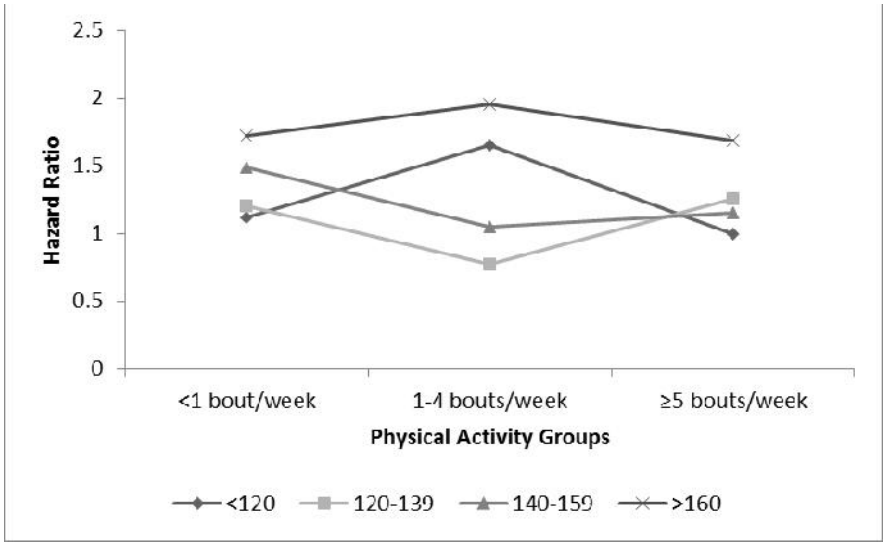
FIGURES

Figure 3.1. Interaction between systolic blood pressure groups and physical activity level on cardiovascular events.



TABLES

Table 3.1. Participant characteristics.

		Physical Activity Groups		
	All	<1 bout/week	1-4 bouts/week	≥5 bouts/week
N	8743	5751	1583	1409
Age (years)	53.5 ± 12.1	53.9 ± 12.4	51.8 ± 11.4	53.1 ± 11.5
Sex (% women)	4979 (57)	3249 (56.5)	942 (59.5)	788 (55.9)
SBP (mmHg)	136.7 (20.2)	137.2 (20.5)	135.7 (19.7)	135.9 (19.7)
DBP (mmHg)	75.6 (11.6)	75.6 (11.6)	75.4 (11.5)	76.3 (11.6)
% Hypertension	2819 (32.2)	1930 (33.6))	463 (29.3)	426 (30.2)
Smoking				
never	3711 (42.5)	2383 (41.4)	729 (40.1)	599 (42.5)
previous smoker	2599 (29.7)	1682 (29.3)	477 (30.1)	440 (31.2)
current smoker	2433 (27.8)	1686 (29.3)	377 (23.8)	370 (26.3)
Family history of hypertension (% yes)	2881 (33)	1988 (34.6)	427 (27)	466 (33.1)
Social Class				
I+II professional/intermediate	2619 (30)	1624 (28.2)	537 (33.9)	458 (17.5)
III non-manual	1360 (15.6)	843 (14.7)	296 (18.7)	221 (15.7)
III manual	2583 (29.5)	1814 (31.5)	405 (25.6)	364 (25.8)
IV+V part skilled/unskilled	2092 (23.9)	1409 (24.5)	330 (20.9)	353 (25.1)

other	89 (1)	61 (1.1)	15 (1)	13 (1)
Medication (% yes)				
BP-lowering	1730 (19.8)	1237 (21.5)	262 (16.6)	231 (16.4)
Lipid-lowering	336 (3.8)	252 (4.4)	41 (2.6)	42 (3.1)
CVD Events	995 (11.4)	690 (12)	154 (9.7)	151 (10.7)
All-cause mortality	851 (9.7)	609 (10.6)	131 (8.3)	111 (7.9)
Follow-up (months)				
Mortality	101.7 ± 39.2	99.4 ± 38.9	109.5 ± 39.2	102.3 ± 39.4
CVD	99.5 ± 39.9	97.1 ± 39.6	107.7 ± 40	100.1 ± 39.8

Table 3.2. Hazard ratios and 95% confidence intervals for the main effects of systolic blood pressure and physical activity on CVD.

	Model 1		Model 2	
Systolic Blood Pressure				
<120	Ref		Ref	
120-139	0.93	(0.75, 1.14)	0.84	(0.77, 1.16)
140-159	1.15	(0.93, 1.43)	1.21	(0.91, 1.39)
≥160	1.55	(1.22, 1.96)	1.45	(1.15, 1.84)
Physical Activity				
5+/week	Ref			
1-4/week	0.88	(0.71, 1.11)	0.91	(0.73, 1.14)
<1/week	1.15	(0.96, 1.37)	1.08	(0.90, 1.28)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, family history of hypertension, social class, blood pressure- lowering medications, and lipid-lowering drugs

Table 3.3. Hazard ratios and 95% confidence intervals for the main effects of diastolic blood pressure and physical activity on CVD.

	Model 1		Model 2	
Diastolic Blood Pressure				
<80	Ref		Ref	
80-89	1.11	(0.95, 1.29)	1.13	(0.97, 1.31)
90-99	1.28	(1.04, 1.58)	1.22	(0.99, 1.51)
≥100	1.83	(1.35, 2.47)	1.67	(1.23, 2.26)
Physical Activity				
5+/week	Ref		Ref	
1-4/week	0.90	(0.72, 1.13)	0.92	(0.74, 1,07)
<1/week	1.17	(0.98, 1.39)	1.08	(0.91, 1.23)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, family history of hypertension, social class, blood pressure- lowering medications, and lipid-lowering drugs

Table 3.4. Hazard ratios and 95% confidence intervals for the main effects of systolic blood pressure and physical activity on all-cause mortality.

	Model 1		Model 2	
Systolic Blood Pressure				
<120	Ref		Ref	
120-139	0.827	(0.66, 1.03)	0.88	(0.71,1.01)
140-159	0.91	(0.72, 1.14)	0.96	(0.77, 1.21)
≥160	1.13	(0.88, 1.45)	1.17	(0.91, 1.50)
Physical Activity				
5+/week	Ref		Ref	
1-4/week	1.07	(0.83, 1.38)	1.10	(0.85, 1.42)
<1/week	1.33	(1.09, 1.63)	1.26	(1.03, 1.54)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, family history of hypertension, social class, blood pressure- lowering medications, and lipid-lowering drugs

Table 3.5. Hazard ratios and 95% confidence intervals for the main effects of diastolic blood pressure and physical activity on all-cause mortality.

	Model 1		Model 2	
Diastolic Blood Pressure				
<80	Ref		Ref	
80-89	1.06	(0.90, 1.25)	1.08	(0.92, 1.28)
90-99	1.08	(0.85, 1.37)	1.05	(0.83, 1.33)
≥100	1.62	(1.16, 2.27)	1.52	(1.09, 2.13)
Physical Activity				
5+/week	Ref		Ref	
1-4/week	1.08	(0.84, 1.39)	1.11	(0.86, 1.43)
<1/week	1.35	(1.10, 1.65)	1.26	(1.03, 1.55)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, family history of hypertension, social class, blood pressure- lowering medications, and lipid-lowering drugs

SUPPLEMENTAL MATERIALS

Figure 3S.1. Plot of hazard ratios for the impact of levels of systolic blood pressure on all-cause mortality according to physical activity group; A. < 1 bout per week; B. 1-4 bouts per week; C. 5+ bouts per week

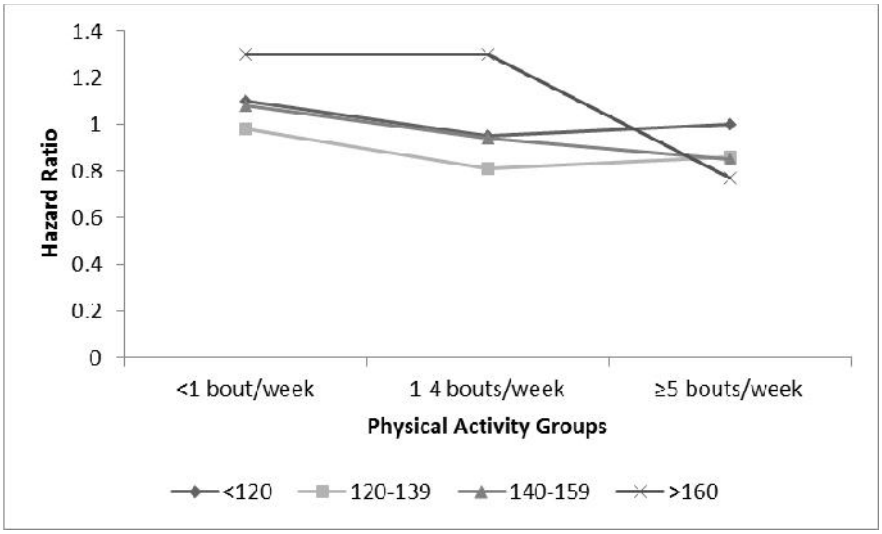


Figure 3S.2. Plot of hazard ratios for the impact of hypertension status on cardiovascular events according to physical activity group; A. < 1 bout per week; B. 1-4 bouts per week; C. 5+ bouts per week. HT: hypertension.

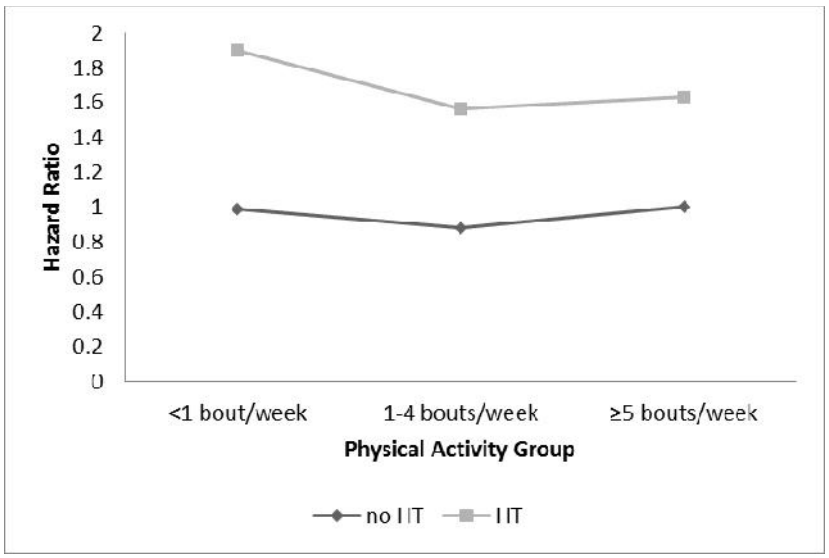
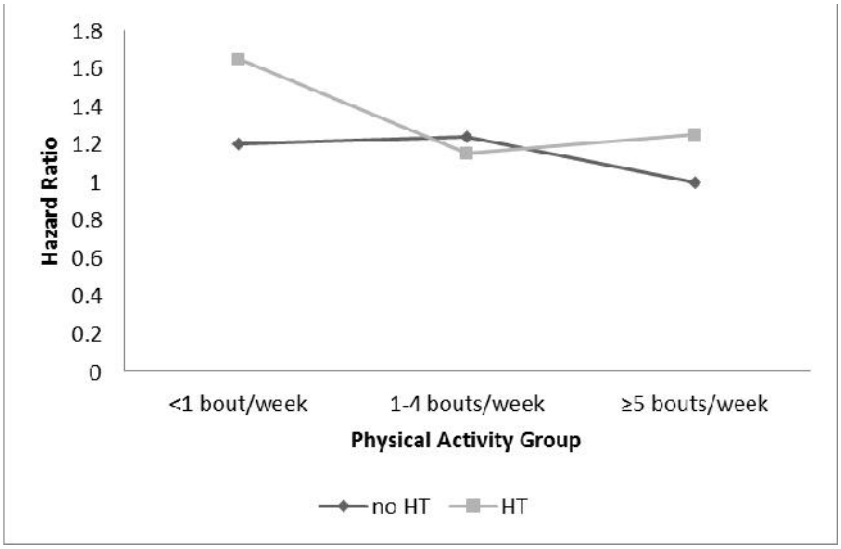


Figure 3S.3. Figure S2. Plot of hazard ratios for the impact of hypertension status on all-cause mortality according to physical activity group; A. < 1 bout per week; B. 1-4 bouts per week; C. 5+ bouts per week. HT: hypertension.



CHAPTER 4 | MARGINAL STRUCTURAL MODELS FOR ESTIMATING THE RELATIONSHIPS BETWEEN PHYSICAL ACTIVITY, BLOOD PRESSURE, AND MORTALITY

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Preamble

To continue building from the missing elements in the systematic review and the interaction analyses, we examined data from the Honolulu Heart Program. This data provides us with the opportunity to examine the relationship between physical activity and blood pressure on CVD events and mortality in the context of a formal causal inference model because of the repeated measurements at multiple time points. These models (i.e., Marginal structural models) take into account time-varying confounders; thus, resulting in a more complete picture of these relationship.

ABSTRACT

Background: The purpose of this study was to evaluate the relationships between physical activity, blood pressure (BP), mortality and major adverse cardiovascular events (MACE). **Methods:** This study comprised analyses of a longitudinal, observational study, the Honolulu Heart Program (n=8006 men). Physical activity (measured by self-report questionnaire) and BP were both assessed at three time points; Exam 1 (1965-68), Exam 2 (1968-71), and Exam 4 (1991-93). Marginal structural Cox models and Marginal structural models for repeated measures were used to estimate: 1) the separate effects of physical activity and BP on mortality and MACE; and 2) the effect of physical activity on BP. **Results:** Being physically active was associated with a reduced rate of mortality (Hazard Ratio (HR) = 0.68, 95% confidence interval (CI) = 0.60 to 0.76) and MACE (HR= 0.84, 95% CI: 0.75 to 0.93) by 32% and 16%, respectively. BP was shown to have a dose-dependent relationship with both mortality and MACE whereby increasing BP was related to more events. Active participants showed a significant decrease of 2.47 mmHg (95%CI, -3.46 to -1.48) in systolic BP compared to the inactive group. No change in diastolic BP was observed. **Conclusions:** We studied the relationships between physical activity, blood pressure, mortality, and MACE, applying novel statistical models which account for covariate variation over time. In conclusion, the results support that being physically active is associated with better outcomes and that BP may be a mediator of the relationship between physical activity and mortality.

INTRODUCTION

Findings have indicated a dose-response association between BP and mortality, where increasing BP increases risk of death, and an inverse dose-response relationship between physical activity and mortality have been demonstrated.(39) A variety of previous studies have shown that physical activity is associated with reduced risk of mortality in people with high BP.(114) These studies have all taken a traditional approach using data collected at a single time point, usually at the point of entry into the study, then followed participants for a determined length of time, censorship point, or death, using standard Cox proportional hazards models to quantify the effects.(114) One issue with these studies is that the models did not account for changes in the exposure (e.g., BP or physical activity) occurring over time, and thus did not allow for understanding how these changes may impact survival.(114)

The purpose of this study was to evaluate the following relationships: 1) the effects of physical activity and BP on mortality and major adverse cardiovascular events (MACE); and 2) the effect of physical activity on BP, while allowing for the exposure and any covariates to change over time. In doing so, a secondary objective was to examine the role of BP as a mediator of the physical activity-survival/MACE relationships. We explored this in the Honolulu Heart Program (HHP) dataset, which followed the same cohort of Japanese-American men for an extended period of time (1965-1994) with multiple follow-up periods between baseline and censorship. We used Marginal structural Cox models (MSCMs) and Marginal structural models (MSMs) for repeated measures to estimate the aforementioned relationships.(134) Unlike Cox models with time-varying exposure and covariates, these recent models are recognized to be appropriate to estimate causal relationships in longitudinal settings when there exists time-dependent confounders that are affected by previous exposure.(44, 135) Under the assumption of

no unmeasured confounders, MSMs allow one to replicate the results that would have been observed under a sequentially randomized experiment when utilizing observational data. However, it would be practically impossible to carry out a true randomized experiment on physical activity with such a long follow-up period. As such, the current study could provide a unique look at the evolving relationships between physical activity, BP, and subsequent, mortality and MACE, which, to our knowledge, no previous studies have done.

METHODS

The Honolulu Heart Program

The HHP is a longitudinal study of 8006 Japanese-American men living on the island of Oahu, Hawaii. Participants were recruited between 1965 and 1968 from a listing of service registrants and were between the ages of 45-68 years.(136) The data collection protocol has been previously described.(137) These secondary analyses of the original dataset are based on four examinations; Exam 1 (1965-68), Exam 2 (1968-1971), Exam 3 (1971-1975) and Exam 4 (1991-1993). All covariates (age, employment status, body mass index, smoking status, and anti-hypertension medication usage) included in the analyses were time-varying. These variables were selected because of their clinical relevance and they were consistently measured across most of the examinations. Approval for these analyses was obtained from the Concordia University Human Ethics Committee (UH2012-025).

Physical Activity

Physical activity was measured at three time points (Exams 1, 2, and 4) by self-report questionnaire. At Exams 1 and 4 participants reported the number of hours/day spent in each of 5 physical activity levels: no physical activity (sleeping, lying down, or reclining); sedentary activity (sitting or standing); slight activity (casual walking); moderate activity (gardening or light carpentry); and heavy activity (lifting, shoveling, or digging). At Exam 2 participants were asked one question about their physical activity at work and one about their physical activity at home using the following responses: "mostly sitting," "moderate," or "much." In order to standardize physical activity across the three time points, we created a binary physical activity variable where participants were defined as active if they reported any moderate or heavy physical activity at Exams 1 and 4 and "moderate" or "much" activity at home or on the job for Exam 2 (see Supplemental Materials for validation of this method).

Blood Pressure

BP was measured at all exams using a mercury manometer by a trained individual (nurse, technician, or physician). Measurements were taken in a resting, seated position. Diastolic BP (DBP) was considered as the fifth Korotkoff sound. For the purposes of these analyses, serial BP measurements were averaged. Additional information regarding BP measurement at each examination is available in the Supplemental Materials.

Surveillance and Outcomes

Mortality and cardiovascular morbidity were continually monitored from the inception of data collection through to the censorship point (December 1994) via hospital admission and discharge records, obituaries, and death certificates. MACE was defined as any fatal or non-fatal myocardial infarction or stroke, coronary artery bypass graft, acute coronary insufficiency, coronary angioplasty, or other cardiac surgeries.

Data treatment

As per recommendation we used age as the time-scale for survival time; that is, survival time was defined as the number of days between birth and death.(138, 139) For individuals who did not die during the study, survival time was right censored at the time of their last examination if they did not attend Exam 4, or at the end of follow-up (December 1994), otherwise. Time to MACE was defined analogously to survival time.

Systolic BP (SBP) and DBP were divided into four categories following standard classifications.(20) Specifically, SBP was categorized as: <120mmHg, 120-139mmHg, 140-159mmHg and ≥160mmHg and DBP as: <80mmHg, 80-89mmHg, 90-99mmHg and ≥100mmHg. For both the MSCMs and the MSMs, we built an augmented dataset where each subject-Exam corresponds to one row. If a row contained missing values for at least one variable required to estimate a given effect, then it was not considered for that estimation (listwise deletion was performed). See Supplemental Materials for each detailed effect estimate.

Building a Directed Acyclic Graph

As suggested by Hernán et al. (2002) we first drew directed acyclic graphs (DAGs) to represent the relationships between all clinically relevant variables using substantive prior knowledge.(140) Two DAGs were created in total; one for the triplet of physical activity, BP, and survival, and another one for the triplet of physical activity, BP, and MACE. The DAGs were created for triplets of variables, instead of producing DAGs for each relationship of interest, in order to examine mediation of the effect of physical activity on each outcome through BP, with each DAG differing only by the outcome (survival or MACE). We assessed the goodness of fit of the proposed DAGs using structural equation models, with minor modifications made to improve fit. For each relationship investigated, we used Pearl's back-door criterion on the final DAGs to identify the set of confounding covariates at each time point.(141) For a brief overview of Pearl's causal graphical framework, we refer the reader to the appendix of VanderWeele and Shpitser.(142) The final DAG equations for survival are detailed in the Supplemental Materials as an example.

The effects of physical activity and BP on the outcomes

We used a MSCM to estimate the effect of current physical activity, that is the physical activity level reported at the most recent exam, on survival and MACE.(143, 144) We used normalized basic stabilized inverse probability of treatment weights in the MSCMs to account for time-dependent confounding, as per the DAGs, using logistic regression models to calculate the weights.(134, 135) Weights were truncated at 100 at each time point to limit the impact of outlying individuals to notably influence the results. We also used MSCMs to estimate the effect

of different levels of BP (SBP, DBP) on survival and MACE. Due to the ordinal nature of the BP exposure covariates, the weights were calculated with ordinal logistic regression models.

The effects of physical activity on BP

We used MSMs for repeated measures to estimate the effect of current physical activity on current SBP and DBP, separately.(145) Our MSMs allowed for the estimation of the effect of the physical activity level reported at a given exam on the BP measured at that same exam, simultaneously for all three exams (>18,000 person-exams). We used both inverse-probability-of-treatment weights and inverse-probability-of-censoring weights to account for time-dependent confounding and censoring.(145) Again we used logistic regression models to calculate the weights, and a similar truncation strategy was adopted.

Statistical Analysis

We used R package LAVAAN to build the DAGs.(146, 147) SAS version 9.2 was used for all other analyses. The PROC PHREG command was used to fit the MSCMs and PROC GENMOD to fit the MSMs for repeated measures.(148)

RESULTS

Participants

The analyses examined 8006 male participants (54 ± 6 years old). Approximately 4% of participants (n=304) had a history of cardiovascular disease (myocardial infarction, stroke, or heart failure) at baseline. The second and forth examinations included 7498 and 3845 participants, respectively. The average length of follow-up was 21.5 years (range: 0.1 years to 33.1 years). A total of 4879 deaths were reported from any cause. There were 1318 cardiovascular deaths and 3279 experienced a MACE. See Table 4.1 for participant characteristics.

Physical Activity, Survival, and MACE

Over 80% of participants were classified as active at baseline (Exam 1), 88% were active at Exam 2, and 75% at Exam 4. The results of the MSCM indicated active individuals had a 32% reduced risk of mortality (Hazard Ratio (HR): 0.68, 95% confidence interval (CI): 0.60-0.76) compared to the inactive participants. Risk of MACE was also significantly decreased in the physically active participants compared to the inactive group (HR= 0.84, 95%CI: 0.75-0.93).

Blood Pressure, Survival, and MACE

Figure 4.1 and Table 4.2 display the results of BP on survival. These demonstrate a dose-response relationship between SBP, DBP and risk of all-cause mortality. The results indicated that higher BP was associated with increased risk of death. Pairwise comparisons showed a

significant difference in risk between all BP groups except for the two lowest SBP categories and between the 80-89 and 90-99 mmHg categories of DBP (see Supplemental Materials).

Similar results were observed for MACE (see Figure 4.2 and Table 4.3). Risk of MACE increased in a dose-dependent manner with higher SBP or DBP, e.g., there was a greater than 60% increased risk for participants with SBP≥160 mmHg compared to the normal BP group. Pairwise comparisons also showed significant differences between SBP groups and DBP groups (see Supplemental Materials).

Physical Activity and Blood Pressure

We observed a significant decrease of 2.47 mmHg (95%CI, -3.46 to -1.48) in SBP between physically active and inactive participants. No change in DBP was observed between the physically active and the inactive groups (0.26 mmHg; 95%CI, -0.22 to 0.75).

Sensitivity analyses

A first sensitivity analysis consisted of repeating the analyses described above, but excluding participants with a history of cardiovascular disease at baseline (n= 304). Also, MSCMs and MSMs for estimating the effect of the cumulative number of exams where participants were physically active were performed. For comparison with the main results and previous findings, we conducted crude analyses that did not account for confounding (i.e., unweighted versions of the MSCMs and MSMs). The results of the sensitivity analyses parallel the main findings above (see Supplemental Materials).

DISCUSSION

To our knowledge, this is the first study to use MSCMs and MSMs to simultaneously report on the effects of BP and physical activity on both survival and MACE, while allowing for time-varying exposure and covariates. The results demonstrated a dose-dependent relationship between BP and the outcomes, mortality and MACE. Additionally, physical activity was found to have a relationship with survival and MACE whereby active individuals had a lower rate of both death and MACE compared to their inactive counterparts. Finally, those who were physically active showed a decrease in SBP but no change in DBP. Taken together, these analyses demonstrated that BP might mediate the physical activity-outcome relationships and the beneficial effects of physical activity on our outcome measures may in part be due to improvements in SBP.

Our analyses build from previous studies which have described a relationship whereby people with lower BP have lower rates of all-cause and cardiovascular mortality.(114) A large individual participant data meta-analysis demonstrated that strong, direct relationship between BP and all-cause and vascular mortality in individuals above 40 years of age.(13) As with BP, our findings regarding physical activity are similar to those noted in association studies.(149) However, to our knowledge, this is the first report to take a formal causal inference perspective to further develop this theory and investigate these relationships whereby participation in physical activity decreases risk of all-cause mortality and MACE. The application of MSMs allowed us to account for changes in BP and physical activity and explore the relationship over time.

Most significantly, the application of MSCMs and MSMs for repeated measures, allowed us to better examine the relationships between these variables. As previously stated, under ideal

circumstances, marginal structural models can replicate the results from a sequentially randomized experiment utilizing observational data. Based on these analyses, we have garnered a more refined understanding of the relationships between physical activity, BP, and our outcomes of interest, mortality and MACE, over an extended follow-up period.

We found a small effect of physical activity on SBP, which was consistent in direction with, but slightly lower than, previous meta-analyses of aerobic exercise intervention studies, where SBP decreases of 3-4 mmHg have been shown.(37) One explanation for this slightly reduced effect may be that the HHP population had higher active levels than modern samples and this may have created a ceiling effect. For example, over 80% of the HHP cohort were defined as active at baseline, compared to 15% of Canadian and 30% of American adults who are active enough to meet current physical activity guidelines.(150, 151) We hypothesized that the effect of physical activity on mortality would be mediated by BP. However, the result above suggests that the mediating effects of BP may be small and that physical activity may improve outcomes through changes in multiple risk factors, which would include BP. For example, physical activity has been shown to help maintain weight, and improve mental health, vascular function, and overall health-related quality of life.(100, 128-130) In addition, evidence suggests that physical activity directly impacts vascular wall function, therefore improving cardiovascular risk beyond traditional risk factor modification. (131)

Two aspects of the current study which we could not assess but would be of interest for future research are the roles of the dose (frequency, intensity, and duration) of physical activity and sedentary behaviours. A more precise, objective measure, e.g., accelerometry, pedometry, or a more discreet self-report scale, e.g., minutes per day of activity vs. hours per day, might have allowed for a better assessment of effects of physical activity, than our discreet measure of

physical activity. This point is especially important because previous,(80, 91) but not all,(152) association studies have shown the physical activity-BP relationship may be intensity-dependent. In addition, sedentary behaviours (defined as any waking activity expending ≤1.5 metabolic equivalents and sitting or reclining posture(153)) which were not captured in the current study due to the required technology not being available, may be another important predictor of outcomes.(154) Sedentary behaviours have been shown to be associated with both cardiovascular and all-cause mortality in adults, independent from physical activity.(155) Thus it is important to further elucidate the role of physical activity intensity and focus on distinguishing between sedentary and activity intensities in the above relationships.

The results of the present series of analyses need to be interpreted within the context of some limitations of the study. Firstly, the causal interpretation of the analyses rest upon the assumption that the DAGs we have built are correct. Even though the final DAGs obtained were supported by the data, they may still not be correct. For instance, some clinically important covariates might not have been included in the DAGs, e.g., sodium consumption, because they were not consistently available in this dataset. Second, the measurement of physical activity (i.e., the questionnaire items) lacked consistency between examination points within the study and not all questions were discreet enough to develop a more comprehensive measure. However, we qualified being physically active as participating in a minimum of one hour per day of moderate activity which exceeds current guidelines and our method of standardizing the physical activity measure was shown to be valid (see Supplemental Materials). Though BP was measured according to standards at the time of assessment, more recent data suggests that automated BP measurement is a more reliable predictor of risk and reduce white coat effect.(156, 157) Therefore, more advanced methods of measuring BP may alter the findings presented herein.

Also, based on the data available, we were unable to track changes in anti-hypertensive medication usage beyond whether or not the individuals were taking medication. For example, we were unable to determine exactly which medication they were taking and whether or not the prescription changed over time (e.g., started treatment with a different class of drug or taking multiple medications). Combination therapy has become increasingly common and can be considered as an indicator of blood pressure control and severity of hypertension (158); thus, whenever possible, it is important to account for changes in medication usage so as not to overestimate the blood pressure-lowering effect of physical activity. It should be noted, however, that limited types of anti-hypertensive medications were available at the inception of the HHP,(159) and combination therapy was not yet recognized at that time.

Another limitation is the inclusion of only men in this cohort. Although no women were included in this study, previous findings suggest there may be sex-differences in the magnitude, but not pattern, with respect to the BP, physical activity, and mortality associations.(39) Whilst several studies have also shown dose-response associations between physical activity and mortality (i.e., increased volume of physical activity is associated with increased life expectancy) we were not able to confirm these because of a lack of consistent information across the follow-up periods.(160, 161) However, our coarse measure of physical activity was able to detect a significant difference in mortality and MACE rates between active and inactive participants. Despite these limitations, there are a number of strengths to this study, notably, the large sample size (8006 men), repeated follow-ups over a long period (> 21 years), and a good retention of participants.

CONCLUSIONS

In summary, our analyses show strong and positive dose-dependent associations between BP and mortality/MACE. Moreover, physical activity was shown to be negatively associated with mortality/MACE. Physical activity and SBP were also found to be negatively associated. Since special attention was given to appropriately dealing with confounding, these associations could be causally interpreted under the assumption of no unmeasured confounders. Taken together, this suggests that physical activity is a determinant of mortality/MACE, with BP mediating the relationship between physical activity and mortality/MACE. Our results thus provide further support for recommending physical activity as a way to reduce risk of mortality/MACE through BP reductions.

CONFLICT OF INTEREST, DISCLOSURES & ACKNOWLEDGEMENTS

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Ethical Approval: Concordia University Human Research Ethics Committee (UH2012-025, 10000588)

FIGURES

Figure 4.1. Hazard ratios for effect of (A) systolic blood pressure and (B) diastolic blood pressure on survival. Error bars represent 95% Confidence Intervals. Dashed line indicates reference level (1.00).

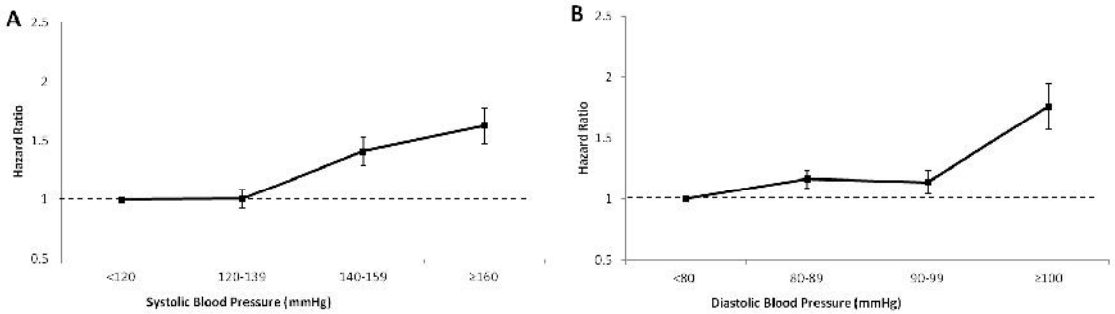
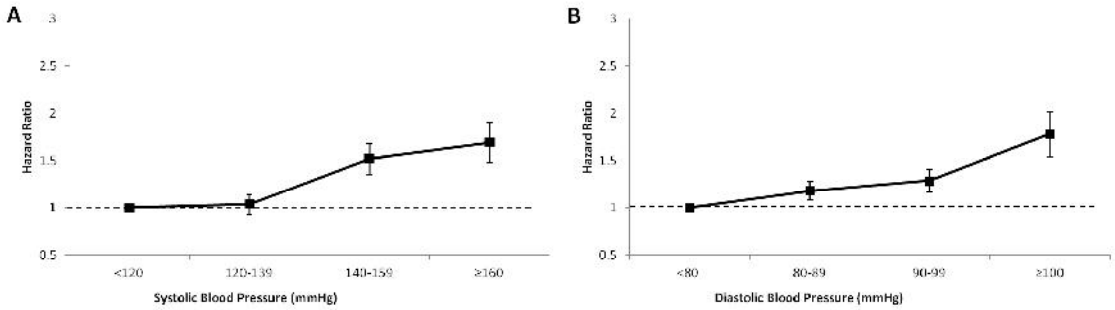


Figure 4.2. Hazard ratios for effect of (A) systolic blood pressure and (B) diastolic blood pressure on Major Adverse Cardiovascular Events. Error bars represent 95% Confidence Intervals. Dashed line indicates reference level (1.00).



TABLES

Table 4.1. Baseline participant characteristics.

Characteristic	Mean ± SD
N	8006
Age (years)	54 ± 6
BMI (kg/m2)	23.8 ± 3.1
Systolic blood pressure (mm Hg)	134 ± 21
Diastolic blood pressure (mm Hg)	82 ± 12
Physical Activity (n)	6494 (81%)
Smoking status (n)	
Never smoker	2409 (30%)
Previous smoker	2094 (26%)
Current smoker	3502 (44%)
History of Cardiovascular Disease (n)	304 (2.5%)

Table 4.2. Risk of all-cause mortality according to systolic and diastolic blood pressure categories.

Systolic Blood Pressure	Hazard Ratio	
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.01	(0.93, 1.09)
140-159 mmHg	1.41	(1.30, 1.53)
≥160 mmHg	1.63	(1.48, 1.79)
Diastolic Blood Pressure	**Hazard Ratio**	
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.16	(1.09, 1.24)
90-99 mmHg	1.14	(1.05, 1.24)
≥100 mmHg	1.76	(1.58, 1.96)

Ref: Reference group.

Table 4.3. Risk of MACE according to systolic and diastolic blood pressure categories.

Systolic Blood Pressure	Hazard Ratio	
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.04	(0.94, 1.15)
140-159 mmHg	1.52	(1.37, 1.70)
≥160 mmHg	1.69	(1.50, 1.92)
Diastolic Blood Pressure	**Hazard Ratio**	
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.18	(1.09, 1.29)
90-99 mmHg	1.29	(1.17, 1.42)
≥100 mmHg	1.78	(1.56, 2.04)

Ref: Reference group.

SUPPLEMENTAL MATERIALS

METHODS

Consistency of the Physical Activity Measurement

In order to test the validity of our approach to classifying physical activity, we built a 2x2 table where individuals were categorized as being active/inactive according to two subjective questionnaires. Participants were classified as active in the first questionnaire if they indicated either much or moderate physical activity at home or on the job. Participants were classified as active in the second questionnaire if they reported spending any time doing moderate physical activity. We used Exam 1 as a reference because both self-report questionnaires were assessed at this time point. Formal analysis indicates 83.7% concordance between these two physical activity questionnaires (κ= 0.42). Therefore, we deemed it appropriate to use this method to create a binary physical activity variable (active/inactive).

Blood Pressure Measurement

Table 4S.1. Blood pressure measurement details at each examination.

Examination	Total number of measurements	Measurement performed by	Arm
Exam 1	3	Nurse (2), Physician (1)	Left
Exam 2	4	Nurse (2), Physician (2)	3 Left, 1 Right
Exam 4	2	N/A	Left

Data Treatment

Table 4S.2. Available data for every effect estimation.

	Exam 1	Exam 2	Exam 4	Total patient-exam
Alive	n = 8,006	n = 7,603	n = 4,330	19,936
SBP ← PA	n = 7,943 (99%)	n = 7,410 (97%)	n = 3,317 (77%)	18,670 (94%)
DBP ← PA	n = 7,943 (99%)	n = 7,410 (97%)	n = 3,313 (77%)	18,666 (94%)
Surv. ← PA	n = 7,911 (99%)	n = 7,410 (97%)	n = 3,406 (79%)	18,727 (94%)
Surv. ← SBP	n = 7,906 (99%)	n = 7,389 (97%)	n = 3,300 (76%)	18,595 (93%)
Surv. ← DBP	n = 7,906 (99%)	n = 7,389 (97%)	n = 3,300 (76%)	18,595 (93%)
Alive and without MACE	n = 8,006	n = 7,463	n = 3,343	18,812
MACE ← PA	n = 7,911 (99%)	n = 7,295 (98%)	n = 2,691 (80%)	17,897 (95%)
MACE ← SBP	n = 7,906 (99%)	n = 7,275 (97%)	n = 2,615 (78%)	17,796 (95%)
MACE ← DBP	n = 7,906 (99%)	n = 7,275 (97%)	n = 2,615 (78%)	17,796 (95%)

DAG Equations

Table 4S.3. DAG equations for survival for each examination point. Directed arrows represent cause-effect relationships. Bi-directed arrows represent an unobserved common cause between the variables. T1= Exam 1; T2= Exam 2; T4= Exam 4; PhysicalActivity= physical activity status; Age= age; Employment= employment status; BMI= Body Mass Index; CurrentSmoker, PreviousSmoker= smoking status (current, previous, never); SystolicBP= systolic blood pressure; DiastolicBP= diastolic blood pressure; Survival= survival; HyperTensTrt= Hypertension medication usage.

Exam 1
PhysicalActivityT1 ← AgeT1
EmployementT1 ← AgeT1
HyperTensTrtT1 ← PhysicalActivityT1 + AgeT1 + EmployementT1 + BMIT1 + CurrentSmokerT1
CurrentSmokerT1 ← AgeT1 + EmployementT1
PreviousSmokerT1 ← AgeT1 + EmployementT1

BMIT1 ← PhysicalActivityT1 + AgeT1

DiastolicBPT1 ← PhysicalActivityT1 + AgeT1 + EmployementT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1

SystolicBPT1 ← PhysicalActivityT1 + AgeT1 + EmployementT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1

- SystolicBPT1 + DiastolicBPT1 + PhysicalActivityT1 + Age1 + EmployementT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1

CurrentSmokerT1 ↔ PreviousSmokerT1

PhysicalActivityT1 ↔ EmployementT1

HyperTensTrtT1 ↔ DiastolicBPT1

HyperTensTrtT1 ↔ SystolicBPT1

BMIT1 ↔ CurrentSmokerT1

BMIT1↔ PreviousSmokerT1

Exam 2
PhysicalActivityT2 ← HyperTensTrtT1+ PhysicalActivityT1 + BMIT1 + AgeT2 + EmployementT2 EmployementT2 ← EmployementT1+ AgeT2 - SystolicBPT1 + DiastolicBPT1 + HyperTensTrtT1 + PhysicalActivityT2 +AgeT2 + EmployementT2 + BMIT2 + CurrentSmokerT2 CurrentSmokerT2 ← CurrentSmokerT1 + PreviousSmokerT1 + AgeT2 + EmployementT2 PreviousSmokerT2 ← CurrentSmokerT1 + PreviousSmokerT1 + AgeT2 + EmployementT2 BMIT2 ← PhysicalActivityT1 + BMIT1 + PhysicalActivityT2 + AgeT2 – DiastolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1 PhysicalActivityT2 + AgeT2 + EmployementT2 + BMIT2 + CurrentSmokerT2 +PreviousSmokerT2 - SystolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1 + PhysicalActivityT2 + AgeT2 + EmployementT2 + BMIT2 +CurrentSmokerT2 + PreviousSmokerT2

- SystolicBPT1 + DiastolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + BMIT1 + CurrentSmokerT1 + PreviousSmokerT1 + SystolicBPT2 + DiastolicBPT2 + PhysicalActivityT2 + AgeT2 + EmployementT2 + BMIT2 + CurrentSmokerT2 + PreviousSmokerT2 CurrentSmokerT2 ↔ PreviousSmokerT2 HyperTensTrtT2 ↔ DiastolicBPT2 HyperTensTrtT2 ↔ SystolicBPT2 BMIT2 ↔ CurrentSmokerT2 BMIT2 ↔ PreviousSmokerT2
Exam 4
PhysicalActivityT4 ← HyperTensTrtT1 + PhysicalActivityT1 + HyperTensTrtT2 + PhysicalActivityT2 + BMIT2 + AgeT4 EmployementT4 ← EmployementT1 + EmployementT2 + AgeT4 - SystolicBPT1+ DiastolicBPT1 + HyperTensTrtT1 + SystolicBPT2 + DiastolicBPT2 + HyperTensTrtT2 + BMIT2 +

PhysicalActivityT4 + AgeT4 + EmployementT4 + BMIT4 + CurrentSmokerT4

CurrentSmokerT4 ← CurrentSmokerT1 + PreviousSmokerT1 + CurrentSmokerT2 + PreviousSmokerT2 + AgeT4 + EmployementT4

PreviousSmokerT4 ← CurrentSmokerT1 + PreviousSmokerT1+ CurrentSmokerT2 + PreviousSmokerT2 + EmployementT4

BMIT4 ← PhysicalActivityT1 + BMIT1 + PhysicalActivityT2 + BMIT2 + PhysicalActivityT4 + AgeT4

– DiastolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + CurrentSmokerT1 + PreviousSmokerT1

+ DiastolicBPT2 + HyperTensTrtT2 + PhysicalActivityT2 + BMIT2 + CurrentSmokerT2 + PreviousSmokerT2

+ PhysicalActivityT4 + AgeT4 + EmployementT4 + BMIT4 + CurrentSmokerT4 + PreviousSmokerT4

- SystolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + CurrentSmokerT1+ PreviousSmokerT1

+ SystolicBPT2 + HyperTensTrtT2 + PhysicalActivityT2 + BMIT2 + CurrentSmokerT2 + PreviousSmokerT2

+ PhysicalActivityT4 + AgeT4 + EmployementT4 + BMIT4 +CurrentSmokerT4 + PreviousSmokerT4 +

ystolicBPT1 + DiastolicBPT1 + HyperTensTrtT1 + PhysicalActivityT1 + CurrentSmokerT1 + PreviousSmokerT1

+ SystolicBPT2 + DiastolicBPT2 + HyperTensTrtT2 + PhysicalActivityT2 + BMIT2 + CurrentSmokerT2

+ PreviousSmokerT2 + SystolicBPT4 + DiastolicBPT4+ PhysicalActivityT4 + AgeT4 + EmployementT4 + BMIT4

+ CurrentSmokerT4 + PreviousSmokerT4

CurrentSmokerT4 ↔ PreviousSmokerT4

PhysicalActivityT4 ↔ EmployementT4

HyperTensTrtT4 ↔ DiastolicBPT4

HyperTensTrtT4 ↔ SystolicBPT4

BMIT4 ↔ CurrentSmokerT4

BMIT4 ↔ PreviousSmokerT4

RESULTS

Table 4S.4. Results of pairwise comparisons for systolic and diastolic blood pressure on survival.

Comparison Systolic Blood Pressure Groups			Hazard Ratio	p
≥160 mmHg	vs.	140-159 mmHg	1.15	0.0017
≥160 mmHg	vs.	120-139 mmHg	1.61	<.0001
≥160 mmHg	vs.	<120 mmHg	1.63	<.0001
140-159 mmHg	vs.	120-139 mmHg	1.40	<.0001
140-159 mmHg	vs.	<120 mmHg	1.41	<.0001
120-139 mmHg	vs.	<120 mmHg	1.01	0.8293
Comparison Diastolic Blood Pressure Groups			Hazard Ratio	p
≥100 mmHg	vs.	90-99 mmHg	1.55	<.0001
≥100 mmHg	vs.	80-89 mmHg	1.51	<.0001
≥100 mmHg	vs.	<80 mmHg	1.76	<.0001
90-99 mmHg	vs.	80-89 mmHg	0.98	0.6146
90-99 mmHg	vs.	<80 mmHg	1.14	0.0023
80-89 mmHg	vs.	<80 mmHg	1.16	<.0001

Table 4S.5. Results of pairwise comparisons for systolic and diastolic blood pressure on MACE.

Comparison Systolic Blood Pressure Groups			Hazard Ratio	p
≥160 mmHg	vs.	140-159 mmHg	1.11	0.0713
≥160 mmHg	vs.	120-139 mmHg	1.63	<.0001
≥160 mmHg	vs.	<120 mmHg	1.69	<.0001
140-159 mmHg	vs.	120-139 mmHg	1.46	<.0001
140-159 mmHg	vs.	<120 mmHg	1.52	<.0001
120-139 mmHg	vs.	<120 mmHg	1.04	0.4193
Comparison Diastolic Blood Pressure Groups			Hazard Ratio	p
≥100 mmHg	vs.	90-99 mmHg	1.39	<.0001
≥100 mmHg	vs.	80-89 mmHg	1.51	<.0001
≥100 mmHg	vs.	<80 mmHg	1.78	<.0001
90-99 mmHg	vs.	80-89 mmHg	1.09	0.0918
90-99 mmHg	vs.	<80 mmHg	1.29	<.0001
80-89 mmHg	vs.	<80 mmHg	1.18	<.0001

Sensitivity Analysis

The results below are those for the analyses excluding participants with a history of CVD at baseline (n= 304). Note: these findings are similar to those reported in the whole sample.

Physical Activity, Survival and MACE

The results of the causal analysis indicate active individuals had a reduced rate of mortality (HR: 0.78, 95%CI: 0.71 to 0.85) compared to the inactive participants. Risk of MACE was also significantly decreased in the physically active participants compared to the inactive group (HR= 0.86, 95%CI: 0.76 to 0.97).

Physical Activity and Blood Pressure

There was a significant decrease of 2.34 mmHg (95%CI, -3.35 to -1.33) in SBP between physically active and inactive participants. No change in DBP was observed between the physically active group and the inactive in either model (0.39 mmHg; 95%CI, -0.10 to 0.88).

Blood Pressure

Table 4S.6. Risk of all-cause mortality according to systolic and diastolic blood pressure categories excluding participants with CVD at baseline.

Systolic Blood Pressure	Hazard Ratio	
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.01	(0.93, 1.09)
140-159 mmHg	1.40	(1.28, 1.52)
≥160 mmHg	1.63	(1.48, 1.80)
Diastolic Blood Pressure		
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.16	(1.09, 1.25)
90-99 mmHg	1.14	(1.05, 1.25)
≥100 mmHg	1.75	(1.56, 1.96)

Ref: Reference group.

Table 4S.7. Risk of MACE according to systolic and diastolic blood pressure categories excluding participants with CVD at baseline.

Systolic Blood Pressure	Hazard Ratio	
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.042	(0.94, 1.15)
140-159 mmHg	1.52	(1.36, 1.69)
≥160 mmHg	1.68	(1.48, 1.91)
Diastolic Blood Pressure		
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.23	(1.13, 1.34)
90-99 mmHg	1.36	(1.22,1.51)
≥100 mmHg	1.77	(1.54, 2.05)

Ref: Reference group.

Table 4S.8. Results of pairwise comparisons for systolic and diastolic blood pressure on survival excluding participants with CVD at baseline.

Systolic Blood Pressure			Hazard Ratio	p
≥160 mmHg	vs.	140-159 mmHg	1.168	0.0010
≥160 mmHg	vs.	120-139 mmHg	1.621	<.0001
≥160 mmHg	vs.	<120 mmHg	1.632	<.0001
140-159 mmHg	vs.	120-139 mmHg	1.388	<.0001
140-159 mmHg	vs.	<120 mmHg	1.398	<.0001
120-139 mmHg	vs.	<120 mmHg	1.007	0.8605
Diastolic Blood Pressure			Hazard Ratio	p
≥100 mmHg	vs.	90-99 mmHg	1.532	<.0001
≥100 mmHg	vs.	80-89 mmHg	1.500	<.0001
≥100 mmHg	vs.	<80 mmHg	1.749	<.0001
90-99 mmHg	vs.	80-89 mmHg	0.979	0.6436
90-99 mmHg	vs.	<80 mmHg	1.142	0.0025
80-89 mmHg	vs.	<80 mmHg	1.166	<.0001

Table 4S.9. Results of pairwise comparisons for systolic and diastolic blood pressure on MACE excluding participants with CVD at baseline.

Comparison Systolic Blood Pressure Groups			Hazard Ratio	p
≥160 mmHg	vs.	140-159 mmHg	1.107	0.1004
≥160 mmHg	vs.	120-139 mmHg	1.612	<.0001
≥160 mmHg	vs.	<120 mmHg	1.679	<.0001
140-159 mmHg	vs.	120-139 mmHg	1.456	<.0001
140-159 mmHg	vs.	<120 mmHg	1.516	<.0001
120-139 mmHg	vs.	<120 mmHg	1.042	0.4340
Comparison Diastolic Blood Pressure Groups			Hazard Ratio	p
≥100 mmHg	vs.	90-99 mmHg	1.306	0.0006
≥100 mmHg	vs.	80-89 mmHg	1.441	<.0001
≥100 mmHg	vs.	<80 mmHg	1.772	<.0001
90-99 mmHg	vs.	80-89 mmHg	1.104	0.0567
90-99 mmHg	vs.	<80 mmHg	1.357	<.0001
80-89 mmHg	vs.	<80 mmHg	1.230	<.0001

Crude Results

The results below are the crude results obtained using an unweighted version of the MSCMs and MSMs.

Physical Activity, Survival, and MACE

The crude results show that active individuals had a reduced rate of mortality (HR: 0.72, 95%CI: 0.70 to 0.78) compared to the inactive participants. Risk of MACE was also significantly decreased in the physically active participants compared to the inactive group (HR= 0.76, 95%CI: 0.69 to 0.84).

Physical Activity and Blood Pressure

There was a significant decrease of 2.76 mmHg (95%CI, -3.71 to -1.81) in SBP between physically active and inactive participants. No change in DBP was observed between the physically active group and the inactive group (-0.06 mmHg; 95%CI, -0.55 to 0.43).

Table 4S.10. Crude results for risk of all-cause mortality according to systolic and diastolic blood pressure categories.

Systolic Blood Pressure	Hazard Ratio	95%CI
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.10	(1.01, 1.20)
140-159 mmHg	1.39	(1.27,1.51)
≥160 mmHg	1.59	(1.44, 1.74)

Diastolic Blood Pressure	Hazard Ratio	95%CI
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.06	(0.99, 1.14)
90-99 mmHg	1.14	(1.05, 1.24)
≥100 mmHg	1.54	(1.38, 1.71)

HR: Hazard Ratio. 95%CI: 95% Confidence Interval. Ref: Reference group.

Table 4S.11. Crude results for risk of MACE according to systolic and diastolic blood pressure categories.

Systolic Blood Pressure	Hazard Ratio	95%CI
<120 mmHg	1.00 (Ref)	
120-139 mmHg	1.47	(1.32, 1.63)
140-159 mmHg	2.24	(2.01, 2.50)
≥160 mmHg	3.17	(2.82, 3.56)

Diastolic Blood Pressure	Hazard Ratio	95%CI
<80 mmHg	1.00 (Ref)	
80-89 mmHg	1.30	(1.20, 1.42)
90-99 mmHg	1.61	(1.46, 1.77)
≥100 mmHg	2.49	(2.22, 2.80)

HR: Hazard Ratio. 95%CI: 95% Confidence Interval. Ref: Reference group.

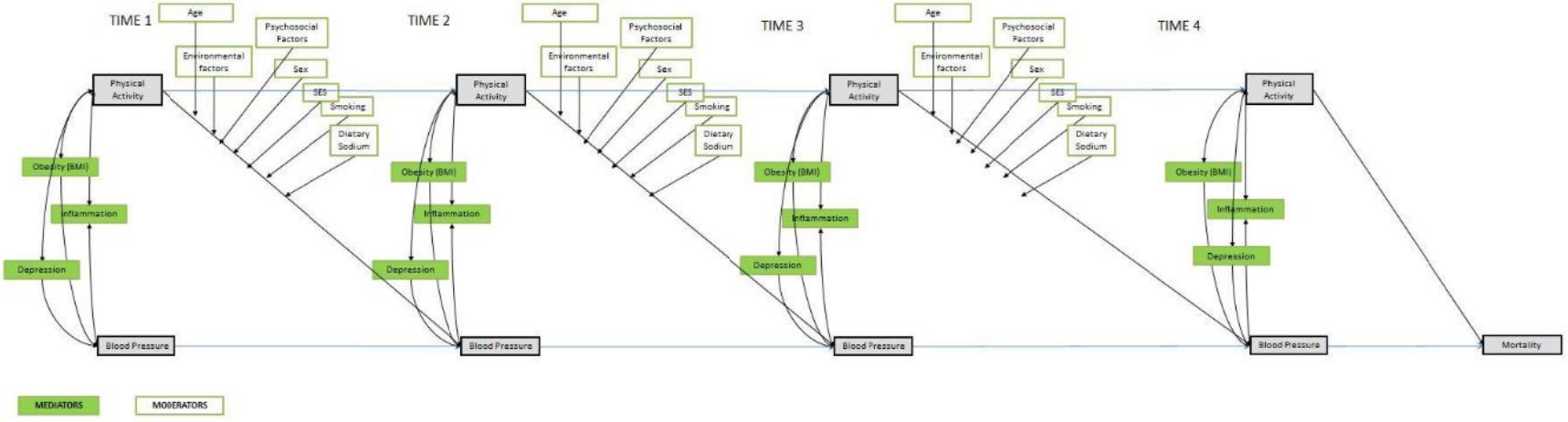
Table 4S.12. Crude results for pairwise comparisons for systolic and diastolic blood pressure on survival.

Systolic Blood Pressure			Hazard Ratio	p
≥160 mmHg	vs.	140-159 mmHg	1.14	0.0019
≥160 mmHg	vs.	120-139 mmHg	1.44	< 0.0001
≥160 mmHg	vs.	<120 mmHg	1.59	< 0.0001
140-159 mmHg	vs.	120-139 mmHg	1.26	< 0.0001
140-159 mmHg	vs.	<120 mmHg	1.39	< 0.0001
120-139 mmHg	vs.	<120 mmHg	1.10	0.0258
Diastolic Blood Pressure			Hazard Ratio	P
≥100 mmHg	vs.	90-99 mmHg	1.35	< 0.0001
≥100 mmHg	vs.	80-89 mmHg	1.45	< 0.0001
≥100 mmHg	vs.	<80 mmHg	1.54	< 0.0001
90-99 mmHg	vs.	80-89 mmHg	1.07	0.1052
90-99 mmHg	vs.	<80 mmHg	1.14	0.0018
80-89 mmHg	vs.	<80 mmHg	1.06	0.0818

Table 4S.13. Crude results for pairwise comparisons for systolic and diastolic blood pressure on MACE.

Comparison Systolic Blood Pressure Groups			Hazard Ratio	P
≥160 mmHg	vs.	140-159 mmHg	1.41	< 0.0001
≥160 mmHg	vs.	120-139 mmHg	2.16	< 0.0001
≥160 mmHg	vs.	<120 mmHg	3.17	< 0.0001
140-159 mmHg	vs.	120-139 mmHg	1.53	< 0.0001
140-159 mmHg	vs.	<120 mmHg	2.24	< 0.0001
120-139 mmHg	vs.	<120 mmHg	1.47	< 0.0001
Comparison Diastolic Blood Pressure Groups			Hazard Ratio	p
≥100 mmHg	vs.	90-99 mmHg	1.55	< 0.0001
≥100 mmHg	vs.	80-89 mmHg	1.92	< 0.0001
≥100 mmHg	vs.	<80 mmHg	2.49	< 0.0001
90-99 mmHg	vs.	80-89 mmHg	1.24	< 0.0001
90-99 mmHg	vs.	<80 mmHg	1.61	< 0.0001
80-89 mmHg	vs.	<80 mmHg	1.30	< 0.0001

Figure 4S.1. Original DAG.



CHAPTER 5 | DISCUSSION

The main purpose of this thesis was to investigate the relationships between physical activity, blood pressure, and mortality. In order to do so, we first conducted a systematic review to identify and synthesize the literature on this theme.(114) The systematic review of literature identified six articles with over 90,000 participants combined. Based on these studies we concluded that regular physical activity was associated with reduced mortality (all-cause and cardiovascular) in patients with high blood pressure.

Next, we built on the previous literature by conducting analyses examining the interactive effect of physical activity and blood pressure on cardiovascular disease development (both fatal and non-fatal events) and all-cause mortality in a modern cohort. The results of the Scottish Health Survey analyses demonstrated an interaction between physical activity and blood pressure on cardiovascular events, such that doing any level of activity for the blood pressure groups <160 mmHg reduced risk of CVD; however, for those with systolic blood pressure ≥160 mmHg, there was no change in risk. Though we observed independent main effects of blood pressure and physical activity, the findings suggest that the two do not interact to impact mortality or cardiovascular outcomes.

The final study has made major strides in assessing the causal relationships between physical activity, blood pressure and mortality. Using advanced statistical techniques (i.e., Marginal structural Cox models and Marginal structural model for repeated measures) the analyses from the Honolulu Heart Program demonstrated a dose-dependent, causal relationship between blood pressure and mortality and cardiovascular disease development. Similarly, physical activity was also causally related to mortality and cardiovascular disease whereby being physically active reduced risk of death and disease. The results indicate that physical activity is a determinant of mortality and cardiovascular events, and that BP may mediate this relationship.

Taken together, the results of these studies indicate that there is a relationship between physical activity and blood pressure in terms of impacting risk of mortality and CVD. However, nuances in the different measures of physical activity between the SHS and HHP should be recognized. In the SHS, we examined three levels of physical activity, the highest of which equates with current recommendations.(162) In comparison, we were only capable of deriving a more crude binary categorisation (active vs. inactive) in the HHP study. When we combine the results, it is important to acknowledge these differences. There was a clear relationship between physical activity and blood pressure in the HHP. The interaction for CVD events in the SHS showed that for lower levels of blood pressure (systolic blood pressure <160 mmHg) doing any physical activity was protective of CVD risk, which is consisted with the HHP, but not for mortality. From these findings, we might assess that volume of physical activity is an important determinant of this relationship (at some levels of blood pressure), and needs to be further explored.

The consideration of time-dependent variables in the HHP is a very novel and compelling feature of the study and adds strength to the findings. A report by Petersen et al. (163) who examined the impact of changes in physical activity over time (i.e., difference in physical activity at time one vs. time two) showed that decreased physical activity with time increased the risk of myocardial infarction, ischemic heart disease and mortality, and conversely that an increase in activity lowered risk. These results nicely complement our findings and support recommendations for being active throughout the lifecourse.

Another aspect to consider is what levels of blood pressure are most responsive to or protected by physical activity. In the SHS, we noted that the interaction between physical activity and blood pressure, although not fully understood, seemed to be driven by activity patterns in

lower levels of blood pressure; thus, individuals with higher blood pressure may be less protected by physical activity. This is not unlike the findings of Brown et al.(115) who showed no interaction between physical activity, pharmacological antihypertensive treatment and blood pressure control. Meaning that whether or not blood pressure is treated or controlled does not interact with physical activity in hypertension.

Thus, the findings of this thesis further questions the subtleties of these relationships which are important to understand to be able to inform and guide clinical practice. If we return to the initial findings of the systematic review,(114) there were strong associations between physical activity and blood pressure in the context of impacting risk of mortality in populations with high blood pressure. It is equally important to acknowledge that there is strong support for mechanisms by which physical activity directly and indirectly impact blood pressure.

Mechanisms

Although the evidence from two of the three studies in this thesis makes a good case for participation in regular physical activity to maintain a healthy BP and thus reduce negative health outcomes, one study does not provide strong support for this pathway. Disagreement in these studies might be due to the physiological mechanisms by which exercise exerts its effect; i.e., direct vs. indirect effects.

Exercise has been shown to induce favorable changes in hemodynamics mainly as a result of increased shear stress on the luminal wall of the vasculature.(164) Exercise studies have also shown links between Tumor Necrosis Factor-α, Interleukin-6, the sympathetic nervous system and the renin-angiotensin system. Aerobic exercise-induced decreases in vascular resistance maybe mediated by inflammatory markers which influence changes in the sympathetic

nervous system and renin-angiotensin system activity resulting in improved endothelial and vascular function.(11, 94-97) In addition to changes in total peripheral resistance, decreased plasma volume may also play a role.(35) Improvements in endothelial function have also been seen in clinical populations, for example in patients with obesity,(99) or coronary artery disease,(100) as a result of participation in physical activity. Thus, it is likely that many factors, both direct (i.e., direct action on the vasculature) and indirect (e.g., inflammatory markers), contribute to the improvement of BP with exercise training. It is also possible that these pathways may have differentially influenced the populations studied across the thesis. However, given that these potential mechanisms were not measured we cannot comment directly on their relative effects.

Limitations

Certain limitations within the thesis need to be acknowledged. Firstly, all the data regarding physical activity was self-reported, which is subject to 'recall bias' and may be influenced by the participants' health, mood, or other psychological factors.(27) Secondly, certain confounders (e.g., medication usage and dietary sodium) were missing or inadequately reported for inclusion in the models, which could result in overestimation of the effect of physical activity on blood pressure and subsequently hard cardiovascular outcomes. Also, differences between sexes were not evaluated. Lastly, the possibility of selection bias across the thesis should be noted. For example, in the Scottish Health Survey, over 3,000 participants did not consent to follow-up, meaning we cannot establish the relationship between physical activity and outcomes for this portion of the cohort. It is possible that these individuals may have been in poorer health and thus not willing to participate further in the study. Thus, the results may be

confounded in that the effect of physical activity may be overestimated. Also, in the Honolulu Heart Program cohort, the individuals were of Japanese-American descent and recruited specifically from a military service registry, and recorded physical activity levels much higher than in the general population.(150, 151) Despite limited external validity in the Honolulu Heart Program cohort, the homogenous geo-ethnic population, who lived on a remote island may have very well controlled for missing variables which are considered limitations of the available data (e.g., genetic and dietary factors). However, in both cases the sample cohorts may not be representative of the general population, and may over report the effect of physical activity on blood pressure, cardiovascular outcomes, and mortality.

Clinical Implications

The findings of this thesis suggest that physical activity acts with blood pressure in reducing risk of all-cause mortality and cardiovascular events. This outcome supports engagement in physical activity for longevity. There was no benefit, however, of physical activity on individuals with systolic blood pressure ≥160 mmHg. Yet, hypertensive individuals with systolic blood pressure <160 mmHg (i.e., stage 1 hypertension) did benefit from physical activity. We also observed a continuous relationship between physical activity and blood pressure in the HHP. Therefore, physical activity should continue to be recommended to maintain healthy blood pressure. For stage 2 hypertensive patients, physical activity should continue to be recommended given the widespread health benefits of being active.(165) The findings of the causal model indicate that being physically active over time is beneficial, thus activity should be constant throughout the lifecourse. In terms of volume of physical activity, we see in the SHS that there were no significant differences in risk between the groups doing 1-4 bouts/week and 5+ bouts/week; thus, supporting the notion that "some is better than none."

Future Directions

The findings from this thesis indicate there is a causal relationship between physical activity and blood pressure. To further generalize the results presented herein it would be necessary to not only repeat these analysis in various cohorts, but also to harmonize datasets between studies to achieve a global perspective on the issue.(166, 167) The physical activity-blood pressure relationship may be dose-dependent (i.e., higher volume of physical activity may be related to lower blood pressure) and therefore further exploration of physical activity intensity and volume is necessary. The goal being to identify the optimal level of physical activity, across a range of blood pressures and comorbid conditions, in order to inform clinicians and direct public health messaging. For example, findings from intervention studies have shown that moderate intensity exercise was as effective as vigorous intensity in reducing resting blood pressure in individuals with high blood pressure.(168) However, we, as yet, do not know whether the reduction in blood pressure resulting from either moderate or vigorous intensity exercise translate to changes in CVD and mortality. It may be the case that despite producing similar changes in blood pressure, that moderate intensity would not be as efficient as vigorous exercise for changing these longer term outcomes. The ability to harmonise and use the vast amounts of data that already exist is an opportunity to explore questions such as this one, in order to guide health care professionals and the general public. Having a large harmonised dataset would also allow for further expansion of the already complex model presented in the HHP study by including dietary factors (e.g., sodium and alcohol intake), psychological factors (e.g., anxiety, depression), and examining cohorts with both sexes. Expanded models would also be appropriate for examining the effects of other risk factors (e.g., body composition, cholesterol) on mortality and CVD events.

In addition to previous aerobic exercise recommendations for preventing and treating hypertension (2, 53), the 2013 iteration of the Canadian Hypertension Education Program (169) lifestyle recommendation also included a statement on resistance training (see Table 5.1) based on the findings from meta-analyses of RCTs (see Appendix E).(46, 47) However, resistance training has been typically excluded from longitudinal studies. Most have focused heavily on general aerobic activity levels, walking, leisure time, commuting, and occupational activity and/or sport participation. Thus, the association between resistance training and CVD or mortality are unknown. Given that there is no major blood-pressure lowering effect with resistance training, it is unlikely resistance training and blood pressure are related in the context of reducing risk of mortality or CVD. This question, however, remains open to further investigation.

Another matter to consider is sedentary behaviour, defined as any waking activity expending $\leq$ 1.5 metabolic equivalents and sitting or reclining posture,(170) a hot topic in physical activity research at the moment. The total (combined direct and indirect) health care costs of physical inactivity in Canadian adults have been estimated at $6.8 billion.(171) Some literature has shown that sedentary behaviour throughout the day can be hazardous to health.(132) Using time-stamped accelerometry data allows for the luxury of capturing information to identify not only highly active periods of the day but also bouts of excessive inactivity. Additionally, identifying the periods of the day where people might be most inactive is of significant value. A recent report from Statistics Canada on the Canadian Health Measures Survey has shown that half of Canadians' activity takes places between 11:00am and 5:00pm; adults specifically at lunch time and children and adolescents are most active during lunch and afterschool.(172) These periods correspond with off-work hours; intuitively, this makes logical

sense. Such data aids in helping to develop strategies to overcome long stretches of inactivity, e.g., standing desks and pedaling devices, which remain to be tested. Several studies have shown that predominantly sedentary behaviors, *e.g.*, time spent watching television and using motorised transport, predict both cardiovascular and all-cause mortality in adult populations.(173-175) These behaviours are also known to have various negative metabolic consequences,(132, 176-178) even in the short term,(179) and also associated with obesity.(180) Additionally, it has been suggested sedentary behaviours may directly affect vascular function.(132) Beunza et al.(133) have previously shown that self-reported sedentary behaviours (*e.g.*, time spent viewing television, using a computer, driving sleeping, etc.) was associated with almost 50% increased risk of incident hypertension. Therefore it is possible that the pathological mechanisms attributed to sedentary behaviours may be responsible for the detrimental effects of physical inactivity on blood pressure. And so future research should not only focus on the quantity and intensity of physical activity in hypertensive cohorts, but also on sedentary behaviours such as television viewing and driving and objectively measured sedentariness (as measured with accelerometry).

Final Conclusions

The findings from this thesis suggest there is a causal relationship between physical activity and blood pressure, such that physical activity acts with blood pressure in reducing risk of all-cause mortality and cardiovascular events. This outcome supports engagement in physical activity over the lifecourse for longevity and maintenance of healthy blood pressure.

Table 5.1. 2013 Canadian Hypertension Education Program recommendation for physical exercise.(169)

For nonhypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce their BP), prescribe the accumulation of 30-60 minutes of moderate intensity dynamic exercise (eg, walking, jogging, cycling, or swimming) 4-7 days per week in addition to the routine activities of daily living (Grade D). Higher intensities of exercise are not more effective (Grade D). For nonhypertensive or stage 1 hypertensive individuals, the use of resistance or weight training exercise (such as free weight lifting, fixed-weight lifting, or handgrip exercise) does not adversely influence BP (Grade D).

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APPENDIX A

Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. *Journal of Hypertension*. 2012;30(7):1277-88. Wolters Kluwer Health Lippincott Williams & Wilkins©

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The impact of physical activity on mortality in patients with high blood pressure: a systematic review

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See editorial comment on page 1310

Background: Physical activity has been shown to be beneficial for the prevention and management of hypertension. In the general population, physical activity has been shown to decrease mortality.

Purpose: The purpose of this systematic review was to identify and synthesize the literature examining the impact of physical activity on mortality in patients with high blood pressure (BP).

Methods: An extensive search was conducted by two independent authors using Medline, Embase and Cochrane Library electronic databases (between 1985 and January 2012) and manual search from the reference list of relevant articles. Inclusion criteria were as follows: longitudinal design with minimum 1-year follow-up; hypertensive status of the cohort was indicated; and BP, physical activity, and mortality were measured.

Results: Six articles evaluating a combined total of 48 448 men and 47 625 women satisfied the inclusion criteria. Cardiovascular and/or all-cause mortality were shown to be inversely related to physical activity in all studies. For example, patients with high BP who participated in any level of physical activity had a reduced risk (by 16–67%) of cardiovascular mortality, whereas a greater than two-fold increase in risk of mortality was noted in nonactive individuals. However, activity classification and parameters, such as frequency, duration, intensity, and volume, as well as BP status, were not consistent across studies.

Conclusions: Regular physical activity is beneficial for reducing mortality in patients with high BP. More research is needed to establish the impact of specific kinds of physical activity and whether any differences exist between sexes.

Keywords: blood pressure, hypertension, mortality, physical activity, systematic review

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; D&B, Downs and Black; HPA, high physical activity; ICD, International Classification of Diseases; IL-6, interleukin-6; LIFE, Losartan Intervention for Endpoint; LPA, low physical activity; Meds, medications; MONICA, Multinational Monitoring of trends and determinants in Cardiovascular disease; MPA, moderate physical activity; NHANES, National Health and Nutrition Examination Survey; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risk; TNF-α, tumor necrosis factor-α

INTRODUCTION

Hypertension represents the highest proportion of attributable mortality amongst all global risk factors and is a large burden to healthcare systems worldwide [1,2]. There exists a strong, direct relationship between blood pressure and risk of stroke mortality, ischemic heart disease mortality, and all-cause mortality [3].

Current guidelines recommend regular physical activity as a preventive measure and a first-line nonpharmacological treatment for hypertension [4–6]. Habitual leisure time physical activity has been shown to reduce all-cause mortality in both men and women [7]. A study of Harvard alumni showed that those who engaged in regular physical activity lived over a year longer than their sedentary counterparts [8]. Furthermore both leisure time physical activity and occupational activity have shown similar results with respect to reducing risk of death from ischemic heart disease [9]. A review of 44 studies concluded that the volume of physical activity and all-cause mortality are related in an inverse, linear dose-dependent manner [10]. Researchers have also shown that cardiorespiratory fitness, measured by maximal exercise stress testing, is related to mortality [11]. Of note, Blair *et al*. [12] have shown that this is consistent for both normotensive and hypertensive men, in that men with higher cardiorespiratory fitness have a decreased risk of mortality. Moreover, participation in aerobic [13,14] or resistance [15,16] exercise can lead to modest reductions in blood pressure.

Despite the available literature to support the benefits of physical activity on blood pressure and mortality in the general population, it is not clear whether these

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benefits translate to decreases in cardiovascular or all-cause mortality specifically in patients with high blood pressure. Therefore, the purpose of this systematic review is to present the results of prospective longitudinal studies exploring the effect of physical activity on mortality (cardiovascular and all-cause) in patients with high blood pressure.

METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The literature search was conducted using the Medline, Embase and Cochrane Library electronic databases and manual search from the reference list of relevant articles. Records were identified using standardized search terms. The Medline search strategy, as seen below, was adapted according to the respective indexing systems for the Embase and Cochrane Library databases. No previously established review protocol exists for this theme. English language longitudinal studies collecting data from human samples, published between the beginning of January 1985 and the end of January 2012, were considered, without any other limitations. The search and screening phases were conducted independently by two authors (A.R. and A.D.) with the help of two medical librarians, one from McGill University (A.L.) and the other one from Concordia University (D.K.). Any discrepancies were resolved through consensus. All the authors participated in the final selection of the included studies. Data were extracted by one author (A.R.) using an electronic form and checked for accuracy (A.D.). All authors have reviewed the extracted data. Variables of interest included: study and participant characteristics (e.g. length of follow-up, age, etc.), blood pressure and physical activity measurement tools and classification schemes, method of mortality and cause of death verification, cardiovascular and all-cause mortality hazard ratios as well as study-specific covariates.

Medline search strategy:

1. Hypertension/or hypertens*.mp.
2. blood pressure.mp. or Blood Pressure/
3. Normotens*.mp.
4. Arterial pressure.mp.
5. 1 or 2 or 3 or 4
6. Exercise/ or exercise.mp.
7. physical active*.mp.
8. physical* active.mp.
9. Motor Activity/
10. resistance training.mp. or Resistance Training/
11. exercise*.mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. Mortality/
14. Death/
15. Fatal Outcome/
16. 13 or 14 or 15
17. 5 and 12 and 16
18. Limit 17 to (English language and humans and yr = '1985-Current')

Retrieved records were retained if they fit all of the following criteria: longitudinal design with a minimum 1-year follow-up; adult participants (>18 years of age) had high blood pressure or hypertensive status was indicated; and blood pressure, physical activity and cardiovascular or all-cause mortality were measured.

Risk of bias was evaluated in the selected studies using a modified version of the Downs and Black [18] tool so that only questions pertinent to prospective cohort studies were retained. This same method has been used previously [19,20]. Thus 15 of the original 27 items (reporting: 1–4, 6, 7, 9, 10; external validity: 11–13; internal validity: 16–18, and 20) were considered for a possible total score of 15, in which a higher score indicates better quality publication. Additionally, funnel plots were used to evaluate publication bias. In cases when group sample sizes were not detailed in the original article, efforts were made to contact the authors by telephone and E-mail; however, identifying current contact information was not always possible.

A meta-analysis would have allowed us to quantify the overall effect of physical activity on mortality in this population. However, there was a substantial lack of consistency in the reporting of physical activity, whereby each study was classified in a different manner according to varying criteria in the self-report questionnaires, which made formal statistical analysis impractical. For instance, some studies classified physical activity groups according to the number of steps or city blocks walked each day, whereas other studies used minutes per day, metabolic equivalent scales or kilocalories per day to categorize the participants.

RESULTS

A total of 3217 records were retrieved (see Fig. 1). Of the 26 full-text articles [7,8,11,12,21–42] evaluated for eligibility, 20 were eliminated for the following reasons; in one article [24] the analysis was based on a sub-sample of a larger trial [32] included in the systematic review, two articles [12,35] did not measure leisure time physical activity (only fitness or work activity were evaluated), and the remaining 17 studies [7,8,11,21–23,25–29,33,34,36,38,40,41] reported collecting data relating to blood pressure, physical activity, or mortality, but they did not evaluate the relationship between the three variables. Usually, physical activity and blood pressure were considered covariates in these reports. Thus, six studies were identified. Table 1 describes the characteristics of these studies. Altogether these studies evaluated 48 448 men and 47 625 women for a total of 96 073 adults. Of the six studies, two considered only male participants [30,39] and the remaining four included both men and women [31,32,37,42]. Only three studies [32,37,42] reported results for men and women separately. The cohorts originated from Northern Europe (Denmark, Sweden, Iceland, Norway, Finland and the UK) or USA. Medication usage was only indicated for the Losartan Intervention for Endpoint (LIFE) trial [32]. None of the other studies reported the type of medications, apart from stating that participants using blood pressure-lowering drugs were included and classified as hypertensive. Vatten *et al.* [42] stated that participants with specific comorbidities were excluded, including patients using antihypertensive

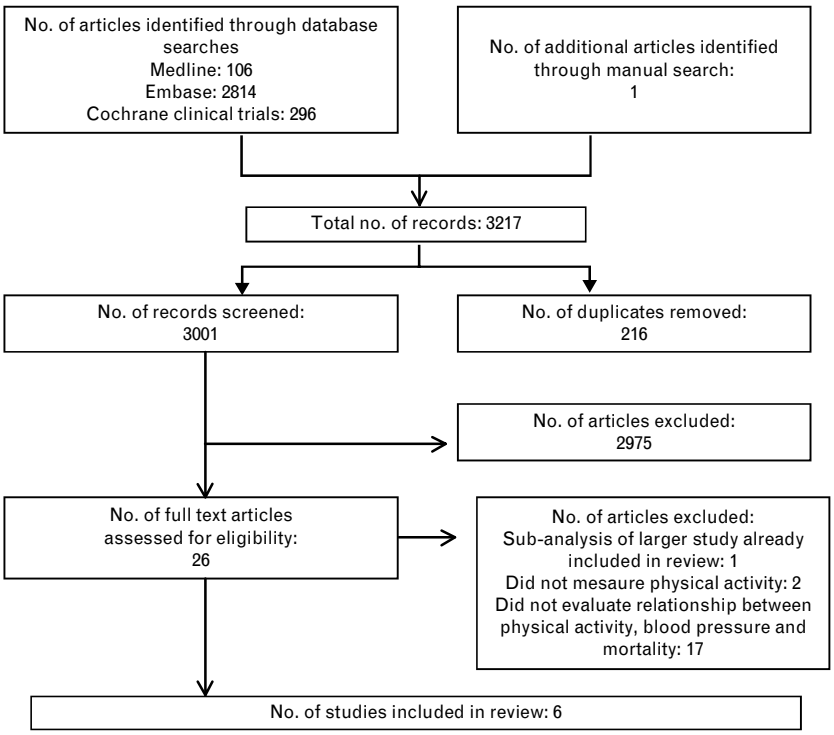

FIGURE 1 Literature search results.

medications. Exclusions were also specified for the LIFE trial recruitment [32]. By design, the LIFE cohort also had left-ventricular hypertrophy [32]. The National Health and Nutrition Examination Survey I (NHANES I) report by Fang *et al.* [31] and LIFE trial, reported by Fossum *et al.* [32], were the only reports to include alcohol consumption and race/ethnicity; additionally NHANES I considered diet and socioeconomic measures in their model for analysis.

Amongst the articles selected are several sub-analyses of larger trials [31,32,37,39]. In cases when information regarding the methods of blood pressure measurement, physical activity assessment, or mortality was not available in the text, the reference list or original publications were consulted.

Blood pressure

Classification

According to the design of this review, each of the selected publications evaluated patients with high blood pressure; however, the criteria used to diagnose hypertension varied between studies. Engström *et al.* [30] used cut-off values of at least 160 mmHg or at least 95 mmHg for SBP and/or DBP, respectively, or self-reported use of antihypertensive medication. Fang *et al.* [31] and Hu *et al.* [37] established their own respective classification schemes (see Table 1). Fossum *et al.* [32] selected participants based on their blood pressure following 2 weeks of placebo treatment. If SBP ranged between 160–200 mmHg and/or 95–115 mmHg they were classified as hypertensive and included in the cohort. In contrast, Vatten *et al.* [42] excluded individuals who reported using blood pressure-lowering medications prior to entering the study. The authors established four categories for SBP (<120 mmHg, 120–139 mmHg, 140–159 mmHg, >160 mmHg) and DBP (<80 mmHg, 80–89 mmHg, 90–99 mmHg, ≥100 mmHg) classification spanning normotensive and hypertensive values. Paffenbarger *et al.* [39] stated that all participants were hypertensive; however, they did not describe what blood pressure threshold level or criteria were used to define high blood pressure.

Measurement

Details for the measurement of blood pressure can be found in Table 2. Three studies [30,31,42] reported measuring blood pressure with a manual sphygmomanometer according to a defined protocol [43]. Engström *et al.* [30], Fossum *et al.* [32,44,45] and Fang *et al.* [31] specifically reported the patients to be in a seated position; however, Paffenbarger *et al.* [39] and Vatten *et al.* [42] did not describe the posture of the participants. The LIFE trial reports indicate a standardized protocol was used to measure blood pressure [44,45]. Hu *et al.* [37,46] described all but one of their multiple sites to have measured blood pressure in the seated position; this single site evaluated patients in a recumbent position [46]. Although the method of blood pressure measurement was consistent within each participating site, the WHO Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) blood pressure assessment document [46] explained that both random-zero sphygmomanometers and simple

TABLE 1. Study and sample characteristics

First author (year)	Country	Study	Follow-up (years)	*N*	Sex (female/male)	Baseline age (years)	BMI (kg/m^2)	Comorbid conditions[a]	Meds[b]	D&B score
Engström (1999) [30]	Sweden	–	23.8 (1968/69-death/December 1993)	642	0/642	55	24.5–24.5	No CVD	No	11
Fang (2005) [31]	USA	National Health and Nutrition Examination Survey (NHANES I)	11.8–17 (1971/1975–June 1992)	9791	6011/3780	38–55	22.8–27.04	No exclusions indicated	No	12
Fossum (2007) [32]	Denmark, Finland, Iceland, Norway, Sweden, United Kingdom, USA	Losartan Intervention for Endpoint (LIFE)	4.8	9185	4961/4224	66–67	27.4–29.1	Left ventricular hypertrophy	Yes	10
Hu (2007) [37]	Finland	–	6.6–31.7; mean: 19.9 (1972–2003)	26643	12244/14399	41–51	26.1–28.6	No exclusions indicated	No	13
Paffenbarger (1991) [39]	USA	College Alumni Health Study, University of Pennsylvania Cohort II	24 (1962–1985)	819	0/819	–	–	No exclusions indicated	No	8
Vatten (2006) [42]	Norway	Nord Trøndelag Health Study (HUNT)	16 (1984/86-death/December 2002)	48993	24409/24584	$\geq$ 20	–	Excluded participants	No	13

BMI, body mass index; CVD, cardiovascular disease; D&B, Downs and Black [18]; Meds, medications.
[a]Indicates if patients with comorbid diseases were included in the study.
[b]Indicates whether or not the participants' medication use was reported.

sphygmomanometers were used. Details regarding measurement of blood pressure in the University of Pennsylvania College Alumni cohort [39] were not available.

Physical activity assessment

Classification

At baseline, the LIFE cohort [32] classified participants as sedentary (never active), intermediate ($\leq$30 min of activity/week), or active (>30 min/week) based on responses to their questionnaire. Engström *et al.* [30] conducted structured interviews and following an initial classification (almost completely inactive, some, regular and regular hard activity) they collapsed the groups into nonvigorous (i.e. inactive and some activity) and vigorous (i.e. regular and regular hard activity) groups. Fang *et al.* [31] asked their participants two questions regarding physical activity: 'Do you get much exercise in things you do for recreation, or hardly any exercise, or in between?' and 'In your usual day, aside from recreation, how active are you?' The MONICA cohort [37] qualified their occupational and leisure time physical activity as low, moderate, or high based on descriptors given for each respective type of physical activity. Additionally, commuting physical activity was classified as motorized, walk/cycle less than 30 min or walk/cycle at least 30 min. Based on information collected about the number of city blocks walked per day, number of stairs climbed daily and the type and frequency of sport or recreational activities, Paffenbarger *et al.* [39] calculated a physical activity index which estimated the amount of kilocalories expended per week. However, for this analysis they only used a classification scheme according to level of sport participation. Vatten *et al.* [42] collected subjective information on the frequency of exercise, average duration of each session, activity intensity and based on responses graded participants into the following hierarchy: no activity, low, medium and high. Engström *et al.* [30] and Fang *et al.* [31] used descriptive categories, whereas the remaining studies attempted to quantify physical activity by time [32,37,42] or by type and frequency of exercise [39,42].

Measurement

Information regarding physical activity was obtained through self-report in all studies. Engström *et al.* [30] conducted interviews with their participants, whereas all other studies reported using questionnaires [31,32,37,39,42]. General and leisure time physical activity were the main types of activity considered; however, Hu *et al.* [37] also collected information specifically relating to occupational and commuting physical activity (these results are not presented here). Each study established a classification scheme for activity levels (see Table 2).

Follow-up and mortality

The length of follow-up ranged from almost 5 years up to 24 years. Cardiovascular mortality [30–32,37,42] and all-cause mortality [30–32,39] were evaluated in the selected studies. Most studies obtained a confirmation of

TABLE 2. Summary of methods and classification schemes for selected studies

First author (year)	Blood pressure		Physical activity		Mortality and cause of death
	Classification	Measurement	Classification	Measurement	
Engström (1999) [30]	Hypertension SBP ≥ 160 mmHg or DBP ≥ 95 mmHg or reported using antihypertensive medication	Morning, seated position, measured to nearest 5 mmHg with mercury sphygmomanometer and 12 x 16 rubber cuff	Non-vigorous: Inactive (group 1) + some activity (group 2); vigorous: regularly active (group 3) + regular hard activity (group 4)	Structured interview	Mortality Register, Swedish National Bureau of Statistics; ICD, 8th and 9th revision
Fang (2005) [31]	Normal BP: no history of hypertension and BP <120/80 mmHg; prehypertension: no history of hypertension and BP 120–139/80–89 mmHg; hypertension: history of hypertension, reported using antihypertensive medication, BP ≥140/90 mmHg	Seated position, with weekly calibrated manometer and falling pressure at 2–3 mmHg, measured to nearest 2 mmHg [43]	Recreational activity: 1. low activity; 2. moderate activity; 3. high activity	Self-report questionnaire; only considered 'recreational activity'	Death certificate or proxy respondent; ICD, 9th revision
Fossum (2007) [32]	Hypertension; SBP 160–200 mmHg and/or DBP 95–115 mmHg after 2 weeks of placebo treatment	Seated position following a standardized protocol [44,45]	Sedentary: never active; intermediate: ≤30min/week; Active: >30 min/week	Self-report questionnaire	Deaths were reported separately and directly to the independent data and safety monitoring board for validation [47]
Hu (2007) [37]	Hypertension: SBP ≥140 or DBP ≥90, using or approved reimbursement for antihypertensive medication; Moderate or severe hypertension: SBP ≥160 or DBP ≥95	Varied across sites (mainly seated position), simple or random-zero sphygmomanometer [46]	Low: almost completely inactive; moderate: some physical activity >4 h/week; high: vigorous activity >3 h/week	Self-report questionnaire; leisure time physical activity	Statistics Finland; ICD, 8th, 9th, and 10th revision
Paffenbarger (1991) [39]	–	–	Sport participation: none, light only, light and vigorous, vigorous only	Self-report questionnaire; only sport participation	–
Vatten (2006) [42]	Blood pressure groups: SBP: <120, 120–139, 140–159, ≥160 mmHg; DBP: <80, 80–89, 90–99, ≥100 mmHg	Calibrated mercury manometers, standard cuff size, measured to the nearest 2 mmHg	1. no activity; and three equal activity groups; 2. low, 3. medium, and 4. high	Self-report questionnaire	Cause of Death Registry, Norway

ICD, International Classification of Diseases.

death through their respective national registries or official documentation [30,31,37,42,47]. No information was provided regarding how mortality data was acquired for the study by Paffenbarger *et al.* [39].

The results from each study (all based on multivariate analyses) as well as the variables included in the respective statistical models are illustrated in Table 3. In hypertensive patients who engaged in vigorous physical activity (i.e.

TABLE 3. Summary of cardiovascular and all-cause mortality results for selected studies

First author (year)	Cardiovascular mortality	All-cause mortality	Multivariate model*
Engström [30] (1999)	Relative risk (95% CI): hypertensive/vigorous physical activity: 0.33 (0.11–0.94); hypertensive/nonvigorous physical activity: 1.00; normotensive/vigorous physical activity: 0.72 (0.39–1.35); normotensive/nonvigorous physical activity: 1.00	Relative risk (95% CI): hypertensive/vigorous physical activity: 0.43 (0.22–0.82); hypertensive/nonvigorous physical activity: 1.00; normotensive/vigorous physical activity: 0.89 (0.60–1.31); normotensive/nonvigorous physical activity: 1.00	Normotensive: smoking; hypertensive: smoking, antihypertensive therapy and SBP
Fang [31] (2005)	Hazard ratios (95% CI): Normotensive: LPA 1, MPA 0.76 (0.39–1.49), HPA 0.65 (0.24–1.77); prehypertensive: LPA 1, MPA 0.79 (0.58–1.09), HPA 0.89 (0.61–1.31); hypertensive: LPA 1, MPA 0.84 (0.73–0.97), 0.80 (0.66–0.96)	Hazard ratios (95% CI): normotensive: LPA 1, MPA 0.75(0.53–1.05), HPA 0.71 (0.45–1.12); prehypertensive: LPA 1, MPA 0.79 (0.65–0.97), HPA 0.93 (0.74–1.18); hypertensive: LPA 1, MPA 0.88 (0.80–0.98), HPA 0.83 (0.72–0.95)	Age, sex, race, BMI, education, diabetes, smoking, alcohol, dietary caloric, sodium, calcium and potassium intake, SBP and serum cholesterol
Fossum [32] (2007)	Hazard ratios (95% CI) Sedentary: reference; intermediate: 0.80 (0.63–1.01); active: 0.49 (0.39–0.62) Men Sedentary: reference; intermediate: 0.65 (0.47–0.90); active: 0.45 (0.33–0.61) Women Sedentary: reference; intermediate: 1.029 (0.73–1.44); active: 0.55 (0.38–0.79)	Hazard ratios (95% CI) Sedentary: reference; intermediate: 0.85 (0.71–1.02); active: 0.65(0.55–0.77) Men Sedentary: reference; intermediate: 0.77 (0.60–1.00); active: 0.60 (0.48–0.76) Women Sedentary: reference; intermediate: 0.95 (0.74–1.24); active: 0.72 (0.56–0.92)	Baseline current smoking, alcohol, sex, age, race, left-ventricular hypertrophy, Framingham risk score†
Hu [37] (2007)	Hazard ratios (95% CI) – men: Low 1, Mod 0.84 (0.77–0.91), High 0.73 (0.62–0.86); trend $P < 0.001$; women: Low 1, Mod 0.78 (0.70–0.87), High 0.74 (0.58–0.94); trend $P < 0.001$	–	Age, study year, education, alcohol, smoking, BMI, SBP, cholesterol, antihypertensive drug use and diabetes
Paffenbarger [39] (1991)	–	Relative risk: none 1.00, light only 1.00, light and vigorous 0.73, vigorous only 0.63, trend $P = 0.1276$	Adjusted for age
Vatten [42] (2006) †	Relative risk (95% CI): high, medium, low, no activity Men <120 mmHg: 0.68 (0.43–1.07), 0.99 (0.70–1.39), 0.78 (0.51–1.20), 1.15 (0.72–1.85) 120–139 mmHg: 1.00 (Reference), 1.06 (0.86–1.32), 0.99 (0.78–1.26), 1.31 (1.02–1.67) 140–159 mmHg: 1.21 (0.97–1.52), 1.25 (1.02–1.55), 1.39 (1.11–1.74), 1.73 (1.37–2.19) >160 mmHg: 1.82 (1.46–2.28), 1.76 (1.42–2.17), 1.84 (1.45–2.34), 2.24 (1.78–2.83) Women <120 mmHg: 0.52 (0.28–0.97), 1.00 (0.61–1.65), 1.08 (0.62–1.86), 1.43 (1.84–2.44) 120–139 mmHg: 1.00 (Reference), 1.12 (0.80–1.57), 1.18 (0.81–1.73), 1.79 (1.26–2.53) 140–159 mmHg: 1.47 (1.04–2.09), 1.54 (1.12–2.12), 1.66 (1.17–2.34), 1.93 (1.39–2.69) >160 mmHg: 1.77 (1.26–2.54), 2.49 (1.84–3.37), 2.60 (1.87–3.60), 2.41 (1.76–3.30)	–	Age, BMI, marital status, education, alcohol and smoking

Data presented herein are results from multivariate analyses for all studies; unadjusted results are not shown in this table. †Only results for SBP are presented here; a similar pattern for DBP was observed [42]. HPA, high physical activity; LPA, low physical activity; MPA, moderate physical activity.

regularly active + regular hard activity), Engström *et al.* [30] found a significant lower risk of all-cause mortality [relative risk (RR) 0.43, 95% confidence interval (CI) 0.22, 0.82] and cardiovascular mortality (RR 0.33, 95% CI 0.11, 0.94) when compared with hypertensive patients who did not engage in vigorous physical activity. The same authors found that level of physical activity did not make a difference in mortality amongst normotensive participants [30]. Fang *et al.* [31] showed that patients with prehypertension who were active for less than 30 min/day (hazard ratio = 0.79, 95% CI 0.65, 0.97), but not those with higher levels of physical activity (hazard ratio = 0.93, 95% CI 0.74, 1.18), had a decreased risk of all-cause mortality. In hypertensive patients, active individuals had a 14–20% lower risk of cardiovascular death and similarly 12–17% lower all-cause mortality risk compared to their least active counterparts.

Overall, the active group from the LIFE [32] sample had a significant decrease in cardiovascular mortality compared to the sedentary group. A nonsignificant decrease of 20% was noted for those who participated in 30 min or less of activity/week. Compared to the sedentary groups, active men (hazard ratio = 0.45, 95% CI 0.33–0.61) and women (hazard ratio = 0.55, 95% CI 0.38–0.79) had a reduced risk of cardiovascular death. Men participating in 30 min/week or less of physical activity also had lower risk of cardiovascular mortality (hazard ratio = 0.65, 95% CI 0.47–0.90); however, there was no difference for moderately active women. Similar results were observed for all-cause mortality.

Hu *et al.* [37] demonstrated that hypertensive patients who engaged in moderate (some activity >4 h/week) or high (vigorous activity >3 h/week) levels of leisure time physical activity had a graded lower risk of cardiovascular death than those who engaged in the lowest category of leisure time physical activity. Of note, similar results were observed in separate analyses for both sexes. Men and women who engaged in moderate activity had a 16 and 22% lower risk of cardiovascular mortality, respectively. Likewise, the most active groups showed further reductions in risk, totalling 27 and 26% decreased risk of cardiovascular death for men and women, respectively. The results from the University of Pennsylvania College Alumni cohort indicated that hypertensive patients who engaged in combined light and vigorous sport participation had a 27% reduced risk of all-cause mortality [39]. Additionally, Paffenbarger *et al.* [39] found that the men who engaged in only vigorous sport participation displayed a 37% decrease in all-cause death. No decrease in mortality was observed with participation in only light activities [39].

An extensive analysis by Vatten *et al.* [42] stratified risk across four categories of blood pressure and four levels of physical activity for both men and women, SBP and DBP alike, ultimately showed that regular physical activity was beneficial for patients with moderate hypertension in terms of lowering cardiovascular risk. Generally, the data displayed a pattern of increased risk with increasing blood pressure categories (SBP and DBP) and decreasing levels of physical activity. The participants in the highest blood pressure group (SBP >160 mmHg) who were inactive displayed greater than double the risk (men: RR 2.24, 95% CI 1.78, 2.83; women: RR 2.41, 95% CI 1.76, 3.30) of cardiovascular mortality compared to very active participants with lower blood pressure. Thus, all six studies have shown an inverse relationship between physical activity and cardiovascular or all-cause mortality.

Risk of bias assessment and publication bias

The results of this evaluation can be found in Table 1. Final scores ranged between 8 and 13 [mean ± standard deviation (SD) 11.4 ± 1.9, median 12). Four studies received high scores (≥12/15). Overall the studies rated well in the reporting category, with an average of seven of eight questions receiving full points. The studies received poor scores for external validity (average 1 point out of 3). Information regarding the representativeness of the sample was generally unavailable. Additionally, whether or not the type of care provided was typical for the patients was not addressed. Three of the four questions assessing internal validity were given full points for each article. When appropriate, most studies did indicate if analysis was adjusted for the length of follow-up. There was no discernable difference in reported outcome between the high and low-scoring studies. Figure 2 is a funnel plot of sample size and log hazard ratio for all studies which provided individual group sample sizes [30–32,37,42]. Generally, the sample sizes for each group varied (lowest $n = 31$, highest $n = 7689$). Overall there is no recognizable difference in symmetry for both cardiovascular and all-cause mortality, which suggests the absence of publication bias.

DISCUSSION

This systematic review examined the impact of physical activity on cardiovascular and all-cause mortality in patients with high blood pressure. An extensive literature search yielded six studies which addressed this question in prospective cohorts. Overall, the studies indicated that physical activity was inversely related with mortality in hypertensive patients, meaning patients with hypertension who were more active showed a lower cardiovascular (16–67% decrease) and all-cause (17–57% decrease) mortality. The results indicated that inactive men and women with high SBP had more than double the risk of cardiovascular death.

Mechanisms

Physical activity has been shown to have an inverse relationship with blood pressure, as well as other cardiovascular disease risk factors and mortality in the general population [7,8,48]. Previous studies examining physical activity have demonstrated up to nearly 40% decreased risk of mortality in women and 35% decreased risk in men across all age groups [7]. The results of this systematic review also showed that this statement is true for patients with elevated blood pressure and/or hypertension. However, the mechanisms by which physical activity may exert this effect remain unclear. Meta-analyses have indicated that regular aerobic exercise [13,14,49] and resistance training [15,16] decrease blood pressure between 2 and 6 mmHg. Similar modest decreases in blood pressure have been shown to decrease risk of cardiovascular events and

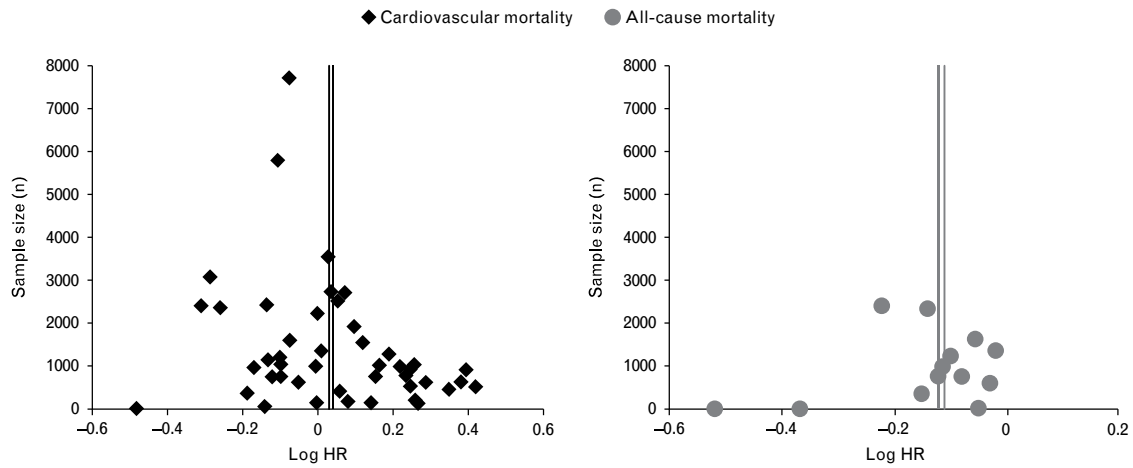

FIGURE 2 Funnel plots of sample size versus log Hazard ratio (HR) in 46 groups for cardiovascular mortality (diamond markers, black lines) and 12 groups for all-cause mortality (round markers, grey lines). Solid vertical lines represent the mean log HR and dashed vertical lines indicate the median log HR.

cardiovascular mortality [50] by magnitudes comparable to those observed with physical activity in this review. Thus it is possible that the blood pressure-lowering effect of regular physical activity and exercise can account for decreases in cardiovascular and all-cause mortality. Yet, the effects of physical activity on mortality may be concomitantly exerted through the reduction of other cardiovascular risk factors, for example, improved glucose tolerance [51], lower BMI [52], reduced platelet activity [53], and reducing risk of comorbid diseases, for example, type 2 diabetes mellitus [54]. A review by Arakawa [55] highlighted changes in total peripheral resistance and a decrease in plasma volume and/or cardiac index as possible mechanisms, amongst several others, though there is not enough evidence available to draw strong conclusions. Fagard [56] has also suggested a decrease in vascular resistance, driven by the sympathetic nervous system and renin–angiotensin systems, as the main mechanism by which aerobic exercise reduces blood pressure. Patients with different types of hypertension, for example essential hypertension versus preeclampsia, have an altered inflammatory profile [57,58]. The sympathetic nervous system and renin-angiotensin system are impacted by anti-inflammatory [e.g. interleukin-6 (IL-6)] and pro-inflammatory [e.g. tumor necrosis factor-α (TNF-α)] markers [59]. Moreover, IL-6 and TNF-α can affect endothelial cells and alter vascular function [59], which is also implicated in the pathogenesis of hypertension [60]. Physical activity has been shown to improve endothelial function [61] even in clinical populations, for example, those with obesity [62], coronary artery disease [63], or exaggerated inflammation [64]. Thus these pathways may mediate the benefits of physical activity on blood pressure and mortality.

Other measures of arterial health, for example arterial stiffness, which are inversely related to mortality [65] are also improved with exercise [66]. Improvements have also been observed in hypertensive patients after 4 weeks of aerobic exercise training [67]. Additionally, women who participate in regular physical activity are protected against the typical increases in arterial stiffness seen with aging [68]. Thus the benefits of physical activity in mediating the relationship between blood pressure and mortality are likely a result of changes in cardiovascular risk factors and overall arterial health. Nevertheless, evidence from the eligible reports suggests that physical activity can be employed for the primary prevention and management of hypertension and reducing risk of mortality.

Sex differences

Amongst the six eligible studies, four included women in their sample populations and of those only three indicated risk for men and women separately [32,37,42]. The findings from all studies indicated that physical activity is protective for both men and women with elevated SBP or DBP. These benefits are similar in magnitude for both sexes, where highly active men gain between 27 and 45% reduced risk of cardiovascular mortality and women approximately 26–55% reduced risk. Correspondingly, inactive men with elevated blood pressure have more than double the risk of cardiovascular mortality, whereas the risk for women is almost two and a half times that of the active women with lower blood pressure. However, little to no consideration was given to potential differences between sexes in the remaining cohorts. Sex-related differences are especially important to consider given that the average age of participants ranged from 20 to 66 years and blood pressure has been shown to differ between men and women across the lifespan [69,70]. Through adulthood, women typically have lower blood pressure levels than men [69,70]. However, during menopause and subsequently throughout the following decades, there is a shift in this trend, whereby the difference in incidence of hypertension between sexes narrows and is eventually higher in women [69,70]. Additionally, age-adjusted comparison of the three phases of the NHANES survey has indicated that prevalence of hypertension tends to be higher in adult women compared to adult men [71]. Also, from 1988 to 2000 the change in

prevalence increased in women to a greater extent than in adult men [71]. The mechanisms by which these shifts occur are not yet understood; however, hormonal changes are thought to play a significant role [69,70].

Measurement of physical activity

The influence of the findings of these studies, or any other for that matter, rests in the quality of the measurement tools used to acquire relevant information. In this case, we are concerned with the quantification and classification of physical activity. Physical activity was consistently measured by self-report, whether through questionnaires or a structured interview.

Self-report is a poor measure of physical activity because the data collected are subject to 'recall bias' and can be dependent on the participants' health, mood, and depression amongst other psychological factors [72]. Despite being easy to administer, particularly when collecting data in large cohorts, these methods do not sufficiently capture vital information such as frequency, duration, intensity or volume of activity. Additionally, each of the studies had defined levels of activity based on the information available from their respective questionnaires, as opposed to standardized tools, which may not have been available at the time of data collection. Thus, what may be considered as a high level of activity according to one study, for example at least 30 min of activity per week [24], does not equate with the definition of high activity in another study, for example, vigorous activity for more 3 h/week [37]. These discrepancies make the direct comparison of results across studies virtually impossible and make it very difficult to identify the optimal frequency, duration, intensity, and volume of activity necessary to reduce the risk of death. Despite this shortcoming, the results still consistently indicate that there is a decrease in risk of mortality with increasing levels of activity, no matter how the latter are defined.

Another important aspect to consider when assessing physical activity in large cohorts is the age or age range of participants. Age is a determinant of activity energy expenditure and accordingly, older adults tend to spend most of their active time engaged in low-intensity activities compared to younger age groups [73]. Measurement scales need to be sensitive enough to perceive these patterns. It has been shown that self-report tools validated to measure physical activity in younger adults are erroneous when used in older populations [74]. Thus, tools need to be customized specifically for the populations in question.

To overcome the fundamental flaws inherent in the use of self-report instruments, researchers are now recommending and standardizing the use of objective measures of physical activity, such as accelerometers [75]. These instruments allow better characterization of the key physical activity parameters; frequency, duration, intensity, and volume [76], and if used consistently will allow better comparison between studies. Additionally, accelerometers or similar devices can be worn throughout the waking day and over the course of several days, hence providing an excellent opportunity to capture not only leisure time physical activity, but commuting and occupational activity as well. Albeit, most of the data collected in the cohorts presented here predate the advent of these new technologies; however, moving forward, this should be taken into consideration.

Measurement of blood pressure and hypertension

Another point of inconsistency between the studies was the definition of hypertension. Again, this is likely a result of the recruitment and/or follow-up periods predating standardized guidelines, which have since significantly evolved. However, this adds a level of confusion when comparing the results. For example, the individuals classified as hypertensive in the study by Engström *et al.* [30] (SBP $\geq$160 mmHg and DBP $\geq$95 mmHg) would instead be classified as having 'moderate or severe' hypertension according to the scheme used by Hu *et al.* [37]. As noted in the 2007 Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and European Society of Cardiology [4], previous research has shown that the relationship between SBP and DBP and cardiovascular risk is linear only upwards of 110–115 mmHg and 70–75 mmHg, respectively, thus creating a somewhat arbitrary cut-off point, designating anything above this point as hypertension. Risk of death from ischemic heart disease and stroke is linear upwards of these values and risk of death is increased two-fold for every increase in 20 mmHg for SBP and 10 mmHg for DBP [5]. The grading of isolated systolic hypertension adds yet another level of complexity. Established guidelines vary according to the governing society and are continuously being revised, which has made and will continue to make room for confusion. Though there are differences between European [4], American [5], and Canadian [6] guidelines it is important for researchers to follow recognized guidelines when classifying patients in order to establish some consistency across the literature.

The quality of blood pressure measurement, again likely subject to the era of data collection, was relatively sufficient across the studies, although not always described in the methods [31,32,37,39], and, ultimately, had to be obtained through other sources [43,44,46]. Blood pressure can vary depending on the time of the day measured, the position of the patient, and the type of equipment used [5]; as such, it is important for these details to be specified. In the case of large cohort, multisite trials it is important to standardize measurement techniques and ensure all operators have been properly trained to take accurate measurements using a standardized protocol. It may very well be that clear standardized protocols were followed in the measurement of blood pressure in the studies presented; however, the protocols were generally not well reported.

Limitations

Several limitations warrant consideration. Firstly, no meta-analysis was performed here due to the heterogeneity of the identified studies. Three of the six studies ranked low (<12/15) in the risk of bias assessment. External and internal validity sections were generally rated with poor scores. Additionally, the reporting of general participant

characteristics, such as age, height, weight, race/ethnicity, smoking status, alcohol consumption, and dietary factors, which are important with respect to the prevention and management of hypertension [5], needs to be improved. Of the six studies selected only one, by Fossum *et al.* [32], described the pharmacological agents prescribed to the hypertensive participants. It is valuable for researchers to indicate medication usage so the readers are aware of the other treatments administered to these patients. This should be a standard component of reporting data for hypertensive patients. The major limitations regarding quantification of physical activity, blood pressure classification, and sex differences have been discussed above. The main driving factor for this may be the period in which these data were collected, beginning as early as 1962 [39]. However, moving forward, this information should be considered necessary and methodological concerns should be addressed in future studies. Lastly, all of the selected studies are observational in nature and therefore any conclusions drawn herein do not infer causation. However, given that all of the results of these studies favor physical activity as beneficial for minimizing the risk of mortality related to high blood pressure, we consider this strong support for the role of exercise. To properly judge the causative role of physical activity in minimizing risk of mortality related to elevated blood pressure, randomized controlled trials would be required.

In conclusion, according to the authors' knowledge, this is the first systematic review evaluating the impact of physical activity on mortality in individuals with high blood pressure. Following an exhaustive literature search, six articles were reviewed. Overall, the results indicate that there is an inverse relationship between physical activity and blood pressure in hypertensive patients. More research is warranted to determine the influence of activity frequency, duration, intensity and volume on mortality in participants with high blood pressure.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX B

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A cautionary note concerning the use of stabilized weights in marginal structural models

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Marginal structural models are commonly used to estimate the causal effect of a time-varying treatment in presence of time-dependent confounding. When fitting an MSM to data, the analyst must specify both the structural model for the outcome and the treatment models for the inverse-probability-of-treatment weights. The use of stabilized weights is recommended because they are generally less variable than the standard weights. In this paper, we are concerned with the use of the common stabilized weights when the structural model is specified to only consider partial treatment history, such as the current or most recent treatments. We present various examples of settings where these stabilized weights yield biased inferences while the standard weights do not. These issues are first investigated on the basis of simulated data and subsequently exemplified using data from the Honolulu Heart Program. Unlike common stabilized weights, we find that basic stabilized weights offer some protection against bias in structural models designed to estimate current or most recent treatment effects. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: time-dependent confounding; marginal structural models; inverse-probability weighting; repeated measures; stabilized weights

1. Introduction

Marginal structural models (MSMs) [1–4] are nowadays a common longitudinal data analytical approach for estimating the effects of time-varying treatments in presence of time-dependent confounding [5–11]. When fitting an MSM to data, an analyst faces two important decisions: (i) the specification of the structural model for the outcome, carried out in accordance with the causal contrast of interest and (ii) the specification of the treatment models, which are used to calculate the inverse-probability-of-treatment received at each time point, that is, the weights [5]. For the structural model, a single measure is commonly used to summarize treatment history, such as the treatment received at the last time point, a cumulative measure of the treatment or an indicator of 'ever started treatment' [5, 12]. The covariates included in the treatment models are typically the baseline covariates and the histories of time-varying covariates and prior treatments. Platt *et al.* [12] outline strategies for MSM specifications and introduce a quasi-likelihood information criterion to help with the selection of the structural model on the basis of data.

Stabilized weights are recommended to be used in MSMs in place of the standard weights because they are generally less variable than the latter [3]. The stabilized weights are similar to the standard weights but are commonly defined so that the numerator is the marginal probability of observed treatment history predicted using prior treatments only, while a numerator equal to one is instead used for the standard weights [3–5]. The denominator is the same for both types of weights. In MSMs, it has been shown that,

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when saturated structural models are specified, the treatment effect estimates that result from the use of stabilized or standard weights is the same [4]. In correctly specified unsaturated structural models, however, the estimates differ, but this difference is only due to sampling variability [4].

This note is concerned with the impact of using the common stabilized weights under different and frequently used specifications of the structural model in ordinary MSMs. As such, we focus on the estimation of the causal effect of a static treatment regime, that is, the estimation of the causal effect that a pre-specified treatment regime would have. In contrast, inferences about a dynamic treatment would consist in estimating the causal effect of a treatment regime where the treatment a subject receives at a given time point is decided according to a pre-specified rule, which might involve time-varying covariates and prior treatments. It has already been recommended not to use stabilized weights for estimating the causal effect of dynamic treatments [13]. In the sequel, we present various settings where the common stabilized weights lead to biased structural model parameter estimates while the standard weights do not. This curious (and perhaps unexpected) phenomenon is observed when the structural model targets the effect of the current treatment or the most recent treatments. This result concerns both classical MSMs and MSMs with repeated measures, although MSMs with repeated measures are arguably more susceptible to this type of structural model specification.

The paper is organized as follows. In Section 2, we introduce the notation and review the MSMs. Section 3 focuses on a very simple example that captures the problem presented in this work. In Section 4, we present the description of a simulation study devised to illustrate the potential problems of using the common stabilized weights in MSMs. The results of the simulation study are presented in Section 5. In Section 6, we investigate these issues using data from the Honolulu Heart Program (HHP). In particular, we find that the estimated effect of the current level of physical activity on blood pressure (BP) differs depending on whether standard or stabilized weights are used. We conclude with a short discussion in Section 7.

2. Notation and marginal structural model implementations

In the following, we distinguish between two types of implementations of MSMs: classical and repeated measures.

2.1. Classical marginal structural model

Based on Robins *et al.* [3], we briefly review the classical MSM. In the sequel, we use capital letters to represent random variables and lower-case letters to represent possible realizations (values) of random variables.

Consider a follow-up study consisting of n sampled subjects from a population, along with covariates measured at $K+1$ time points (visits). Let $A_{k,i}$ be subject i's ($i = 1, \dots, n$) treatment level at the kth visit from the start of the follow-up ($k = 0, \dots, K$), and let Y_i be his outcome measured at end of follow-up, that is, $Y_i = Y_{K+1,i}$. For the sake of simplicity, we consider continuous outcome and binary treatment variables (with $A_{k,i} = 1$ if subject i receives treatment at time k and $A_{k,i} = 0$ otherwise). For subject i, $L_{k,i}$ consists of the outcome at time k, $Y_{k,i}$, and the vector of all other measured risk factors for Y_i at time k, $V_{k,i}$, that is, $L_{k,i} = (V_{k,i}, Y_{k,i})$. We suppose that $L_{k,i}$ temporally precedes $A_{k,i}$ for all i and k. Let $\bar{A}_{k,i} = (A_{0,i}, A_{1,i}, ..., A_{k,i})$ be subject i's treatment history through time k, and let $\bar{A}_i = \bar{A}_{K,i}$. We define $\bar{L}_{k,i}$ and $\bar{L}_i$ similarly. Finally, $Y_{\bar{a}k,i}$ is subject i's counterfactual outcome at visit k, that is, the outcome that would have been observed if, possibly contrary to the fact, subject i had received treatment regime $\bar{a}$ instead of his own treatment regime $\bar{a}_i$. Note that $Y_{\bar{a}k,i} = Y_{k,i}\ \forall\ k$ if $\bar{a} = \bar{a}_i$. As in Hernán *et al.* [4], we assume that every subject's data are independently drawn from a common distribution; therefore, we drop subscript i unless it is required for clarity.

The classical MSM is defined as a model for the population's mean of the counterfactual outcome at visit $K+1$ under treatment history $\bar{a}$

$$E[Y_{\bar{a}}] = g(\bar{a}; \gamma), \tag{1}$$

where g is a user-defined function. Possible g functions are $g(\bar{a}; \gamma) = \gamma_0 + \gamma_1 a_K + \cdots + \gamma_{K+1} a_0$, $g(\bar{a}; \gamma) = \gamma_0 + \gamma_1 a_K$, $g(\bar{a}; \gamma) = \gamma_0 + \gamma_1 \text{cum}(\bar{a})$ where $\text{cum}(\bar{a}) = \sum_{k=0}^{K} a_k$ or $g(\bar{a}; \gamma) = \gamma_0 + \gamma_1 I_{\{\text{cum}(\bar{a}) \geqslant 1\}}$. The parameters γ of model (1) encode the causal effect of the treatment history on the last outcome. For example, when selecting $g(\bar{a}; \gamma) = \gamma_0 + \gamma_1 \text{cum}(\bar{a})$, it is hypothesized that the effect of treatment history on the mean outcome increases linearly as a function of the cumulative treatment. Thus, for two treatment regimes

$\bar{a}$ and $\bar{a}'$ being compared, $\gamma_1(\text{cum}(\bar{a}) - \text{cum}(\bar{a}'))$ can be interpreted as the mean difference in outcome Y, that is, $E\left[Y_{\bar{a}} - Y_{\bar{a}'}\right]$. In particular, if $\bar{a} = \{1, 1, \ldots, 1\}$ and $\bar{a}' = \{0, 0, \ldots, 0\}$ —corresponding to the always and never treated regimes, respectively—then the expected difference in outcome is $\gamma_1(K+1)$. Similarly, if $g(\bar{a};\gamma) = \gamma_0 + \gamma_1 a_K$ is selected, then it is hypothesized that the effect of treatment history on the mean outcome only depends on the last treatment. In this case, γ_1 corresponds to the expected difference in outcome when $\bar{a} = \{\cdot, \ldots, \cdot, 1\}$ and $\bar{a}' = \{\cdot, \ldots, \cdot, 0\}$, where symbol $\cdot$ is used to represent either of the two possible levels for treatment. The issues we are concerned with in this paper stem from using structural model specifications such as this one.

The parameters γ of structural model (1) can be consistently estimated using a weighted linear regression model for $E\left[Y|\bar{A}\right]$, where each subject is weighted by the inverse probability of his observed treatment history conditional on covariates and prior treatments. Specifically, the standard weight for subject i is

$$w_i = \left\{ \prod_{k=0}^{K} \frac{1}{P\left(A_k = a_{k,i} | \bar{A}_{k-1} = \bar{a}_{k-1,i}, \bar{L}_k = \bar{l}_{k,i}\right)} \right\}, \qquad i = 1, \ldots, n, \tag{2}$$

where $\bar{A}_{k-1}$ is ignored in the conditioning when $k = 0$. The standard weights w are often highly variable; therefore, it is usually advised to instead use stabilized weights sw, where

$$sw_i = \left\{ \prod_{k=0}^{K} \frac{P\left(A_k = a_{k,i} | \bar{A}_{k-1} = \bar{a}_{k-1,i}\right)}{P\left(A_k = a_{k,i} | \bar{A}_{k-1} = \bar{a}_{k-1,i}, \bar{L}_k = \bar{l}_{k,i}\right)} \right\}. \tag{3}$$

In both (2) and (3), the $\bar{L}$ covariates are selected to ensure that the sequential (conditional) randomized assumption holds [2], that is

$$Y_{\bar{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1}, \bar{L}_k \quad \forall\ \bar{a} \text{ and } k, \tag{4}$$

where $\perp\!\!\!\perp$ symbolizes statistical independence. Perhaps underrealized is that conditioning on $\bar{A}_{k-1}$ in (4) implies that, in addition to $\bar{L}_k$, the previous treatment variables should also be regarded as potential confounding variables. This last remark is crucial for understanding the possible introduction of bias when using stabilized weights sw in MSMs.

2.2. *Marginal structural model with repeated measures*

Instead of modeling the mean counterfactual outcome at the end of follow-up, an MSM with repeated measures [4] aims to model the mean counterfactual outcome at each time $k+1$ ($k = 0, \ldots, K$) as a function of treatment history up to time k, that is

$$E\left[Y_{\bar{a}(k+1)}\right] = g(\bar{a}_k;\gamma). \tag{5}$$

Popular choices of g function for this type of MSM implementation are $g(\bar{a}_k;\gamma) = \gamma_0 + \gamma_1 a_k + \gamma_2 k$, $g(\bar{a}_k;\gamma) = \gamma_0 + \gamma_1 a_k + \gamma_2 a_{k-1} + \gamma_3 k$, $g(\bar{a}_k;\gamma) = \gamma_0 + \gamma_1 \text{cum}(\bar{a}_k) + \gamma_2 k$, where $\text{cum}(\bar{a}_k) = \sum_{t=0}^{k} a_t$ or $g(\bar{a}_k;\gamma) = \gamma_0 + \gamma_1 I_{\{\text{cum}(\bar{a}_k) \geqslant 1\}} + \gamma_2 k$. Model (5) is then fitted using a weighted linear generalized estimating equation (GEE) regression for $E[Y_{k+1}|\bar{A}_k]$, where person-visit $(i, k+1)$ is weighted by its standard or stabilized weight

$$w_{k,i} = \left\{ \prod_{t=0}^{k} \frac{1}{P\left(A_t = a_{t,i} | \bar{A}_{t-1} = \bar{a}_{t-1,i}, \bar{L}_t = \bar{l}_{t,i}\right)} \right\} \quad \text{or} \quad sw_{k,i} = \left\{ \prod_{t=0}^{k} \frac{P\left(A_t = a_{t,i} | \bar{A}_{t-1} = \bar{a}_{t-1,i}\right)}{P\left(A_t = a_{t,i} | \bar{A}_{t-1} = \bar{a}_{t-1,i}, \bar{L}_t = \bar{l}_{t,i}\right)} \right\}, \tag{6}$$

respectively. The choice of covariates $\bar{L}$ to include in these weights must also be dictated by the sequential randomized assumption [4, 14] as follows:

$$Y_{\bar{a}(k+1)} \perp\!\!\!\perp A_t | \bar{A}_{t-1}, \bar{L}_t \quad \forall\ \bar{a} \quad \text{and} \quad k \geqslant t. \tag{7}$$

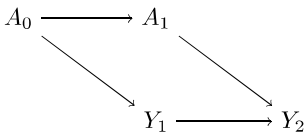

Figure 1. First directed acyclic graph (DAG1).

3. A striking example

The issues raised in this paper are best first illustrated with the simple directed acyclic graph depicted in Figure 1 (DAG1). In DAG1, Y_1 depends on A_0, A_1 depends on A_0, and Y_2 depends on both A_1 and Y_1. Here $L_0 = \emptyset$ and $L_1 = \{Y_1\}$: no L covariates other than the outcome at time one are considered because they are irrelevant to illustrate our problem. Covariates denoted by V are, however, later incorporated in our simulation scenarios presented in Section 4.1.

Consider the implementation of a classical MSM based on data compatible with DAG1. While a first logical step would be the specification of the structural model, we momentarily delay this step and examine the definition of weights w and sw with regard to the sequential randomization assumption (4). Because of the presence of the open back-door path $A_1 \leftarrow A_0 \rightarrow Y_1 \rightarrow Y_2$ ($\bigstar$) from A_1 to Y_2 in DAG1, it follows that $Y_{\bar{a}2} \not\perp\!\!\!\perp A_1$, and therefore the (unconditional) randomization assumption (4) does not hold [15]. This path can be closed by A_0, which leads to $Y_{\bar{a}2} \perp\!\!\!\perp A_1|A_0$. The sequential randomization assumption is achieved conditional on treatment history because for all $\bar{a}$ and $k = 0, 1$, $Y_{\bar{a}} \equiv Y_{\bar{a}2} \perp\!\!\!\perp A_k|\bar{A}_{k-1}$ (we already have $Y_{\bar{a}2} \perp\!\!\!\perp A_0$). In principle, an MSM can thus be validly implemented with the following standard and stabilized weight definitions for subject i:

$$w_i = \frac{1}{P\left(A_0 = a_{0,i}\right)} \times \frac{1}{P\left(A_1 = a_{1,i}|A_0 = a_{0,i}\right)}, \tag{8}$$

and

$$sw_i = \frac{P\left(A_0 = a_{0,i}\right)}{P\left(A_0 = a_{0,i}\right)} \times \frac{P\left(A_1 = a_{1,i}|A_0 = a_{0,i}\right)}{P\left(A_1 = a_{1,i}|A_0 = a_{0,i}\right)} = 1. \tag{9}$$

Note that the second denominators in (8) and (9) could have been set to $P\left(A_1 = a_{1,i}|A_0 = a_{0,i}, Y_1 = y_{1,i}\right)$ to follow the generic notations (2) and (3) for the specification of the weights. However, DAG1 implies that $P\left(A_1 = a_{1,i}|A_0 = a_{0,i}, Y_1 = y_{1,i}\right) = P\left(A_1 = a_{1,i}|A_0 = a_{0,i}\right)$, and thus it suffices to condition on A_0 only.

The simplification of the stabilized weight sw_i to the value 1 in (9) indicates that, in the setting represented by DAG1, *the implementation of a classical MSM with weights sw is equivalent to the implementation of an unweighted (crude) MSM*. This leads to biased or unbiased parameter estimators depending on the form of the structural model selected.

Suppose the structural model $E[Y_{\bar{a}}] = \gamma_0 + \gamma_1 a_1 + \gamma_2 a_0$ is chosen, where parameters γ_1 and γ_2 encode the causal effect of A_1 on $Y_2 \equiv Y$ and of A_0 on $Y_2 \equiv Y$, respectively. Using stabilized weights sw with this structural model yields an unbiased estimator for both γ_1 and γ_2. The parameter γ_1 is of particular interest in this case because, recall, $Y_{\bar{a}2} \not\perp\!\!\!\perp A_1$ due to the open back-door path ($\bigstar$). Although the confounding introduced by this back-door path is not handled by the weights (because $sw_i = 1\ \forall\ i$), it is nonetheless accounted for by the inclusion of the treatment covariate A_0 in the regression model $E\left[Y|\bar{A}\right] = \beta_0 + \beta_1 a_1 + \beta_2 a_0$. This implies that the associational parameter β_1 coincides with the structural parameter γ_1, that is, $\beta_1 = \gamma_1$, as desired.

Suppose we now consider the structural model $E\left[Y_{\bar{a}}\right] = \gamma_0 + \gamma_1 a_1$ and its associated regression model $E\left[Y|\bar{A}\right] = \beta_0 + \beta_1 a_1$. Although this reduced structural model is misspecified because A_0 has an effect on $Y_{\bar{a}2}$, it is much relevant to be able to obtain unbiased estimation for the effect this structural model is capable of identifying, namely, the effect of the most recent exposure effect (A_1) on $Y_{\bar{a}2}$. If the stabilized weights sw are used, then β_1 and γ_1 do not coincide anymore as the confounding is neither accounted for in the weights nor the regression model. With this structural model, unbiased γ_1 estimation can, however, be obtained by using the standard weights w because these weights do account for the confounding caused by A_0.

This example is simple and admittedly a bit artificial because a traditional regression-based approach could have correctly identified the causal effect targeted by the structural model $E[Y_{\bar{a}}] = \gamma_0 + \gamma_1 a_1$ [5]. However, it unravels a potential problem with the use of stabilized weights *sw* along with structural models that only include partial treatment history (e.g., current treatment or current treatment with lag 1 treatment). Indeed, a consequence of such a stabilization of the weights may be that the unconfounding achieved by the denominator is canceled out (at least partially) by the numerator. This phenomenon is empirically demonstrated in Section 5. Also seen in Section 5 is that similar problems occur when using stabilized weights *sw* in MSMs with repeated measures.

4. Description of the simulation study

In this section, we present the four simulation scenarios investigated as well as the definitions of the standard and stabilized weights used in the classical implementation of the MSMs (the weights for the repeated mesures implementation are defined in a similar manner). We conclude the section with a description of the analyses we performed.

4.1. Simulation scenarios

Scenario 1. Our first simulation scenario is compatible with DAG1 (recall Figure 1). The causal relationships between the variables are as follows:

$$\begin{aligned} P\left(A_0 = 1\right) &= 0.5 \\ Y_1 &= A_0 + \varepsilon_{Y_1} \\ P\left(A_1 = 1\right) &= expit(A_0) \\ Y_2 &= A_1 + Y_1 + \varepsilon_{Y_2}, \end{aligned}$$

where $expit(z) = e^z/(e^z + 1)$ and ε_{Y_1} and ε_{Y_2} are independent $N(0, 1)$ random variables. The standard and stabilized weights used in the classical MSM implementation are defined in (8) and (9).

Scenario 2. The second simulation scenario is only slightly more complex than the first scenario (Figure 2):

$$\begin{aligned} P\left(A_0 = 1\right) &= 0.5 \\ Y_1 &= A_0 + \varepsilon_{Y_1} \\ P\left(A_1 = 1\right) &= expit\left(0.5A_0 + 0.5Y_1\right) \\ Y_2 &= A_1 + Y_1 + \varepsilon_{Y_2}, \end{aligned}$$

where ε_{Y_1} and ε_{Y_2} are independent $N(0, 1)$ random variables. In this scenario, the presence of the causal link between Y_1 and A_1 makes the adjustment for Y_1 in the denominator of the weights necessary to achieve (4); the standard and stabilized weights are thus defined as

$$w_i = \frac{1}{P\left(A_0 = a_{0,i}\right)} \times \frac{1}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}\right)},$$

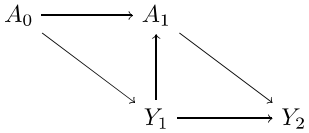

Figure 2. Second directed acyclic graph (Scenario 2).

and

$$sw_i = \frac{P\left(A_0 = a_{0,i}\right)}{P\left(A_0 = a_{0,i}\right)} \times \frac{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}\right)}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}\right)}.$$

Scenario 3. The third scenario is a typical MSM representation and includes a time-dependent confounder V that is affected by previous treatment (Figure 3):

$$\begin{aligned}
V_0 &= \varepsilon_{V_0} \\
P\left(A_0 = 1\right) &= expit\left(0.5V_0\right) \\
Y_1 &= A_0 + V_0 + \varepsilon_{Y_1} \\
V_1 &= 0.5A_0 + \varepsilon_{V_1} \\
P\left(A_1 = 1\right) &= expit\left(0.5A_0 + 0.5Y_1 + 0.5V_1\right) \\
Y_2 &= A_1 + 0.5Y_1 + V_1 + \varepsilon_{Y_2},
\end{aligned}$$

where $\varepsilon_{V_0}, \varepsilon_{Y_1}, \varepsilon_{V_1}$ and ε_{Y_2} are independent $N(0, 1)$ random variables. For this scenario, we adopt the naïve strategy of including all possible covariates for the specification of the weights, that is

$$w_i = \frac{1}{P\left(A_0 = a_{0,i} | V_0 = v_{0,i}\right)} \times \frac{1}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)},$$

and

$$sw_i = \frac{P\left(A_0 = a_{0,i}\right)}{P\left(A_0 = a_{0,i} | V_0 = v_{0,i}\right)} \times \frac{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}\right)}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)}.$$

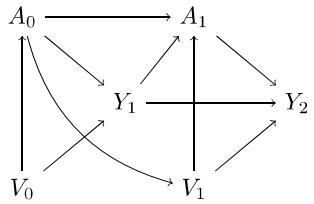

Figure 3. Third directed acyclic graph (Scenario 3).

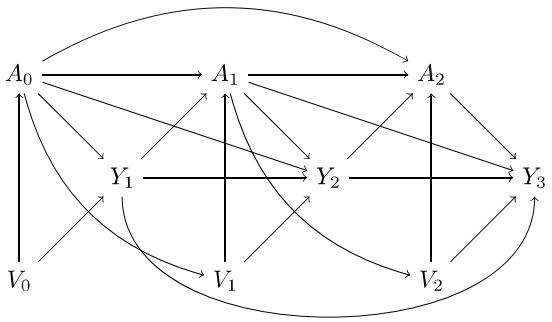

Figure 4. Fourth directed acyclic graph (Scenario 4).

Scenario 4. The fourth scenario is similar to the previous scenario but generates data for an additional follow-up visit (Figure 4):

$$
\begin{aligned}
V_0 &= \varepsilon_{V_0} \\
P\left(A_0 = 1\right) &= expit\left(0.5V_0\right) \\
Y_1 &= A_0 + V_0 + \varepsilon_{Y_1} \\
V_1 &= 0.25A_0 + \varepsilon_{V_1} \\
P\left(A_1 = 1\right) &= expit\left(0.5A_0 + 0.5Y_1 + 0.5V_1\right) \\
Y_2 &= A_1 + 0.25A_0 + 0.5Y_1 + V_1 + \varepsilon_{Y_2} \\
V_2 &= 0.25A_1 + \varepsilon_{V_2} \\
P\left(A_2 = 1\right) &= expit\left(0.5A_1 + 0.3A_0 + 0.5Y_2 + 0.5V_2\right) \\
Y_3 &= A_2 + 0.25A_1 + 0.5Y_2 + 0.5Y_1 + V_2 + \varepsilon_{Y_3},
\end{aligned}
$$

where $\varepsilon_{V_0}, \varepsilon_{Y_1}, \varepsilon_{V_1}, \varepsilon_{Y_2}, \varepsilon_{V_2}$ and ε_{Y_3} are independent $N(0, 1)$ random variables. For this scenario, we also include all possible covariates for the specification of the weights, that is

$$
\begin{aligned}
w_i = &\frac{1}{P\left(A_0 = a_{0,i} | V_0 = v_{0,i}\right)} \times \frac{1}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)} \\
&\times \frac{1}{P\left(A_2 = a_{2,i} | A_1 = a_{1,i}, A_0 = a_{0,i}, Y_2 = y_{2,i}, Y_1 = y_{1,i}, V_2 = v_{2,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)},
\end{aligned}
$$

and

$$
\begin{aligned}
sw_i = &\frac{P\left(A_0 = a_{0,i}\right)}{P\left(A_0 = a_{0,i} | V_0 = v_{0,i}\right)} \times \frac{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}\right)}{P\left(A_1 = a_{1,i} | A_0 = a_{0,i}, Y_1 = y_{1,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)} \\
&\times \frac{P\left(A_2 = a_{2,i} | A_1 = a_{1,i}, A_0 = a_{0,i}\right)}{P\left(A_2 = a_{2,i} | A_1 = a_{1,i}, A_0 = a_{0,i}, Y_2 = y_{2,i}, Y_1 = y_{1,i}, V_2 = v_{2,i}, V_1 = v_{1,i}, V_0 = v_{0,i}\right)}.
\end{aligned}
$$

4.2. Description of analyses

We generated 10,000 datasets of size $n = 1000$ for each of the four scenarios described in Section 4.1. A series of MSM analyses was performed on each dataset. The set of structural models we considered includes a variety of models that have been seen in recent classical and repeated measures MSM implementations [6–11]. For the classical version of the MSMs (*cMSM*), we considered the following three structural models:

- *Full*: $E\left[Y_{\bar{a}}\right] = \gamma_0 + \gamma_1 a_K + \gamma_2 a_{K-1} + \cdots + \gamma_{K+1} a_0$;
- *Current*: $E\left[Y_{\bar{a}}\right] = \gamma_0 + \gamma_1 a_K$;
- *Cumulative*: $E\left[Y_{\bar{a}}\right] = \gamma_0 + \gamma_1 cum(\bar{a})$.

We also considered three structural models for the repeated measures implementation of the MSMs (*rmMSM*):

- *Current*: $E\left[Y_{\bar{a}(k+1)}\right] = \gamma_0 + \gamma_1 a_k + \gamma_2 k$;
- *Current+Lag1*: $E\left[Y_{\bar{a}(k+1)}\right] = \gamma_0 + \gamma_1 a_k + \gamma_2 a_{k-1} + \gamma_3 k$;
- *Cumulative*: $E\left[Y_{\bar{a}(k+1)}\right] = \gamma_0 + \gamma_1 cum(\bar{a}_k) + \gamma_2 k$.

For Scenarios 1–3, the *Full*, *Cumulative* (*cMSM* and *rmMSM*) and *Current+Lag1* structural models are correctly specified. For Scenario 4, only the *Full* and *Cumulative* (*cMSM* and *rmMSM*) structural models are correctly specified. For every scenario and structural model (both *cMSM* and *rmMSM* implementations), the data generating equations presented in Section 4.1 imply that $\gamma_1 = 1$. Recall, however, that γ_1 has different interpretations across structural models (Section 2.1).

We obtained the unweighted results (which is equivalent to setting weights equal to one) as well as the results using the standard and stabilized weights *w* and *sw* for each scenario, implementation and structural model. Specifically, for every combination of implementation/structural model/weight, we estimated the mean and standard deviation of $\hat{\gamma}_1$ based on the 10,000 datasets generated from each scenario. As recommended, we used an independence working correlation structure for the estimation of the GEEs [16, 17]. The analyses were performed using the function `geeglm` from the `R` [18] package `geepack` [19–21].

To comply with `geeglm`'s requirements, for every scenario we fitted the *Current+Lag1* structural model by deleting all the data pertaining to the first visit because the Lag1 treatment (i.e., a_{k-1}) is structurally missing when $k = 0$ [10, 11]. As a by-product of this deletion, the *rmMSM* implementation with the *Current+Lag1* structural model ends up being equivalent to the *cMSM* implementation with the *Full* structural model in the simpler scenarios (Scenarios 1–3).

5. Simulation results

The results of the simulation study are presented in Table I.

We first discuss the results for the classical MSM implementation. As expected, the use of either weights *w* or *sw* with the full structural model (*cMSM Full*) yields unbiased estimates for the true current effect of the treatment on the outcome ($\gamma_1 = 1$) in every scenario. Note that the slight bias of about 1% seen under the more complex Scenario 4 disappears when samples of size 5000 are considered (results not shown). The results for the cumulative structural model (*cMSM Cumulative*) are also unbiased under both types of weights. In Scenarios 1–4, when only the current treatment covariate is included in the structural model (*cMSM Current*), the standard weights *w* yield unbiased γ_1 estimates whereas the stabilized weights *sw* do not.

Now examining the results for the repeated measures MSM implementation, we observe that, as with the classical MSM implementation, the cumulative structural model (*rmMSM Cumulative*) yields unbiased γ_1 estimates under both weights *w* and *sw*. Moreover, the repeated measures MSM with only the current treatment covariate in the model (*rmMSM* Current) similarly yields biased estimates of γ_1 when using stabilized weights *sw*. The repeated measures structural model with current and previous treatments (*rmMSM Current + Lag1*) produces unbiased results for weights *w* and *sw* in Scenarios 1–3 but biased results for weights *sw* in Scenario 4. Unlike results for *cMSM Full*, this bias does not vanish as sample size is increased (the bias remains at 8% when $n = 5000$). This last set of results does not come as a surprise given that Scenario 4 involves three post-baseline visits ($K + 1 = 3$), whereas only two visits ($K + 1 = 2$) are considered in Scenarios 1–3. More precisely, recall that the *Current + Lag1* structural model is not misspecified in Scenarios 1–3, as opposed to Scenario 4.

Table I. Results for Scenarios 1–4 by structural model and marginal structural model (MSM) implementation. The mean and the standard deviation (in parenthesis) of the estimates of γ_1 for each weight definition are provided (calculated from 10,000 datasets of size 1000).

	Classical MSM (*cMSM*)			Repeated measures MSM (*rmMSM*)		
Weight (by scenario):	*Full* ($\gamma_1 = 1$)	*Current* ($\gamma_1 = 1$)	*Cumulative* ($\gamma_1 = 1$)	*Current* ($\gamma_1 = 1$)	*Current+Lag1* ($\gamma_1 = 1$)	*Cumulative* ($\gamma_1 = 1$)
S_1 : 1	0.999 (0.094)	1.243 (0.096)	1.000 (0.057)	1.118 (0.061)	0.999 (0.094)	1.000 (0.053)
S_1 : *w*	0.999 (0.095)	0.999 (0.095)	1.000 (0.058)	0.999 (0.066)	0.999 (0.095)	1.000 (0.054)
S_1 : *sw*	0.999 (0.094)	1.243 (0.096)	1.000 (0.057)	1.118 (0.061)	0.999 (0.094)	1.000 (0.053)
S_2 : 1	1.474 (0.092)	1.681 (0.094)	1.179 (0.057)	1.332 (0.061)	1.474 (0.092)	1.126 (0.053)
S_2 : *w*	1.001 (0.073)	1.000 (0.074)	1.000 (0.054)	1.000 (0.053)	1.001 (0.073)	1.000 (0.051)
S_2 : *sw*	1.001 (0.071)	1.232 (0.078)	1.000 (0.054)	1.113 (0.056)	1.001 (0.071)	1.000 (0.051)
S_3 : 1	1.861 (0.103)	2.168 (0.103)	1.413 (0.061)	1.810 (0.074)	1.861 (0.103)	1.430 (0.056)
S_3 : *w*	1.003 (0.098)	1.002 (0.101)	1.001 (0.072)	1.002 (0.071)	1.003 (0.098)	1.001 (0.062)
S_3 : *sw*	1.003 (0.095)	1.314 (0.102)	1.001 (0.071)	1.153 (0.064)	1.003 (0.095)	1.001 (0.058)
S_4 : 1	2.112 (0.130)	2.900 (0.136)	1.527 (0.054)	2.133 (0.075)	2.061 (0.082)	1.486 (0.048)
S_4 : *w*	1.019 (0.185)	1.011 (0.195)	1.006 (0.110)	1.006 (0.116)	1.011 (0.138)	1.004 (0.085)
S_4 : *sw*	1.013 (0.175)	1.612 (0.193)	1.004 (0.091)	1.282 (0.079)	1.084 (0.097)	1.002 (0.065)

'1', unweighted; *w*, standard weights; *sw*, stabilized weights.

The biased results for weights *sw* under implementation/structural model *cMSM Current*, *rmMSM Current* and *rmMSM Current + Lag1* can be explained using arguments similar to those in Section 3. First, conditioning on the past treatment(s) in the numerators of the stabilized weights *sw* neutralizes some deconfounding acting through the denominators of the weights, and second, the remaining confounding is not handled by the structural model.

It is also worthwhile to mention that, while our analyses focus on parameter γ_1 for simplicity, other parameters of the structural models considered are prone to be estimated with bias when using stabilized weights *sw*. For instance, in Scenario 4, $\hat{\gamma}_2$ is also biased in the implementation/structural model *rmMSM Current + Lag1* when using weights *sw*. Indeed, for this scenario, the mean and standard deviation (in parenthesis) of the 10,000 estimates of $\gamma_2 = 1$ under the three different weighting strategies are (i) unweighted: 1.380 (0.078); (ii) standard weights *w*: 1.007 (0.155); and (iii) stabilized weights *sw*: 1.118 (0.107). The same reasoning as the one put forward for γ_1 explains the bias found when using weights *sw* to estimate γ_2.

To conclude, we observed, from our simulations, that when the structural models were correctly specified, unbiased estimators were obtained when using either stabilized weights *sw* or standard weights *w*. In this case, and as expected, a reduction in variance was also seen for the structural parameter estimators resulting from the use of weights *sw*, as opposed to weights *w*. However, when the structural models were misspecified, only standard weights *w* led to unbiased estimation of the structural parameters. Given that selecting an appropriate structural model is a challenging issue, robustness of the weights to misspecification of this model is believed to be desirable. We feel this is particularly relevant for repeated measures implementations of MSMs, for which simplified structural model specifications could also be preferred to better take advantage of available data (e.g., see [10]). For instance, in our results, remark there is a decrease in variability for the current treatment effect estimator ($\hat{\gamma}_1$) in the *rmMSM Current* implementation/structural model as opposed to the same estimator in the *rmMSM Current + Lag1* implementation/structural model (as a result, in all scenarios, from the use of many more data points for the estimation of this effect in the former structural model).

In the next section, we investigate if other types of stabilized weights would consistently provide unbiased parameter estimates under differentially specified structural models.

5.1. Additional analyses

Although weights *sw* follow the typical definition for stabilized weights found in the MSM literature, other stabilization strategies could be employed. For a classical MSM for instance, basic stabilized weights, which avoid conditioning on the past treatments in the numerators are

$$swb_i = \left\{ \prod_{k=0}^{K} \frac{P\left(A_k = a_{k,i}\right)}{P\left(A_k = a_{k,i} | \bar{A}_{k-1} = \bar{a}_{k-1,i}, \bar{L}_k = \bar{l}_{k,i}\right)} \right\}. \tag{10}$$

For both the classical and repeated measures implementations, we therefore also fitted the MSMs with weights *swb* to verify the impact of such a stabilization strategy on the distribution of $\hat{\gamma}_1$ (Table II). From these results, we observe that all estimates are unbiased and that notable variance reduction can be obtained by using the basic stabilized weights *swb* as opposed to the standard weights *w* (see the results for the repeated measures MSM implementation in particular).

Table II. Results from Scenarios 1–4 by structural model and marginal structural model (MSM) implementation using basic stabilized weights *swb*. The mean and the standard deviation (in parenthesis) of the estimates of γ_1 are provided (calculated from 10,000 datasets of size 1000).

	Classical MSM (*cMSM*)			Repeated measures MSM (*rmMSM*)		
Scenario	*Full* ($\gamma_1 = 1$)	*Current* ($\gamma_1 = 1$)	*Cumulative* ($\gamma_1 = 1$)	*Current* ($\gamma_1 = 1$)	*Current+Lag1* ($\gamma_1 = 1$)	*Cumulative* ($\gamma_1 = 1$)
S_1	0.999 (0.094)	0.999 (0.094)	1.000 (0.058)	1.000 (0.056)	0.999 (0.094)	1.000 (0.053)
S_2	1.001 (0.073)	1.000 (0.074)	1.000 (0.054)	1.000 (0.048)	1.001 (0.073)	1.000 (0.051)
S_3	1.003 (0.098)	1.002 (0.101)	1.001 (0.071)	1.001 (0.060)	1.003 (0.098)	1.001 (0.057)
S_4	1.012 (0.179)	1.008 (0.189)	1.003 (0.092)	1.002 (0.071)	1.006 (0.103)	1.001 (0.062)

6. The Honolulu Heart Program results

In this section, data from the HHP are used to illustrate how the choice of weights can influence the exposure effect estimates in non-simulated MSM analyses.

The HHP is a study of Japanese-American men living in Oahu, Hawaii, which examined 8006 participants. Participants were born between 1900 and 1919 (aged 45-68 years at study entry) and were recruited from the selective service registry. They were evaluated at multiple time points beginning in 1965 and followed until 1994 for deaths and morbid events. Information regarding physical activity participation was collected by questionnaire at Exam 1 (1965–1968), Exam 2 (1968–1971) and Exam 4 (1991–1993). BP was measured manually (in mmHg) by a trained professional during each exam. More details about HHP can be found elsewhere [22].

Repeated measures MSMs were used to estimate the causal effect of physical activity on systolic BP (SBP) and diastolic BP (DBP). Because physical activity was not measured at Exam 3 and because there was a long delay between Exam 2 and Exam 4, we chose to only use data from the first two exams. Our belief is that the effect of current and prior physical activity history on current BP is primarily a function of current physical activity. Our structural model for each type of BP thus has the following form:

$$E\left[Y_{\bar{a}k}\right] = \gamma_0 + \gamma_1 a_k + \gamma_2 k, \tag{11}$$

where unlike Equation (5), which has a delayed treatment effect, the treatment effect in (11) is immediate. In our structural models, $Y_{\bar{a}k}$ is the counterfactual outcome (either SBP or DBP) at Exam k ($k = 1, 2$), and a_k is the physical activity level (active or inactive) reported at Exam k.

For both MSM analyses, the covariates used to calculate the visit specific weights at the first time point (Exam 1) were as follows: age (in years) at Exam 1 and employment at Exam 1 (employed or unemployed). For the second time point (Exam 2), the weights were calculated using the following: employment at Exam 1, physical activity level at Exam 1, hypertension medication usage at Exam 1 (yes or no), body mass index at Exam 1 (in kg/m^2), age at Exam 2 and employment at Exam 2. Note that hypertension medication usage at Exam 1 and body mass index at Exam 1 were not considered in the calculation of the weights at the first time point because these variables are believed to be effects of the physical activity level at Exam 1. Subjects with missing data at a given time point were removed from the analyses (about 1% for Exam 1 and about 3% for Exam 2).

We estimated the effect of current level of physical activity on current SBP and DBP using repeated measures MSMs and the same four weights that were investigated in the simulation studies ('1', *w*, *sw* and *swb*). For the estimation of the GEEs, a robust variance estimator was used along with an independence working correlation structure. The results are summarized in Table III.

Upon the examination of Table III, we remark that the estimates of the effect of current physical activity on current SBP are relatively robust to the choice of weights. However, the choice of weights has a notable impact on the estimates of the effect of physical activity on DBP. In this case, the estimates obtained using an unweighted MSM or an MSM with common stabilized weights *sw* exhibit a significant decrease of DBP with physical activity at level $\alpha = 0.05$, whereas a non-signifiant decrease is obtained from the MSMs with standard weights *w* and basic stabilized weights *swb*. These last results are in accordance with the *rmMSM Current* results from the simulation study where the unweighted and common stabilized weights *sw* estimates departed from those obtained with standard weights *w* and basic stabilized weights *swb*. Because there is believed to be time-dependent confounding, the unweighted repeated measures MSM is considered to be inappropriate for estimating the causal effect of current physical activity on

Table III. Estimated effect of current physical activity level on current systolic (SBP) and diastolic (DBP) blood pressure.

Weights	Estimate for SBP (95% CI)	Estimate for DBP (95% CI)
1	−2.29 (−3.35, −1.22)	−0.82 (−1.40, −0.24)
w	−1.85 (−2.94, −0.75)	−0.43 (−1.04, 0.17)
sw	−1.94 (−3.59, −0.29)	−1.29 (−2.18, −0.39)
swb	−1.56 (−2.56, −0.55)	−0.29 (−0.84, 0.26)

'1', unweighted; *w*, standard weights; *sw*, (common) stabilized weights; *swb*, basic stabilized weights.

current DBP. We also note that the confidence intervals obtained with the basic stabilized weights *swb* are slightly narrower than those obtained with the standard weights *w*.

7. Discussion

Although it is widely known that the weighting scheme affects the variance of MSM estimators, it is less well known that it can also affect their bias. Using a series of simulated examples, we showed that the utilization of the most common stabilized weights (weights *sw*) may lead to biased parameter estimates when structural models feature only partial information on treatment history, such as the current or most recent treatments. The diffusion of this result is critical because such structural model specifications are often seen in repeated measures MSMs, a type of MSMs, which is increasingly used to perform causal inferences [6–11].

The phenomenon documented in this paper adds to the number of subtle issues arising in the implementation of MSMs [5]. Indeed, our results suggest that the choice of weights needs to be carried out according to the structural model that is specified. Particularly, we advise analysts to avoid using the common stabilized weights when the analyses target the estimation of the current or most recent treatment causal effects. In this context, the analysts could adopt the basic stabilized weights *swb* put forward herein, simple weights which have been found to yield unbiased results under all scenarios and structural models investigated.

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APPENDIX C

Talbot D, Atherton J, Lefebvre G, Rossi AM, Bacon SL. Authors' reply to comments on “a cautionary note concerning the use of stabilized weights in marginal structural models”. *Statistics in Medicine*. 2015;34(18):2676-2677

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Authors' reply to comments on 'A cautionary note concerning the use of stabilized weights in marginal structural models'

We would like to thank Dr Taguri for his interest in our work and for providing additional insights regarding the possible bias arising from the estimation of the parameters of misspecified marginal structural models (MSMs) using stabilized weights [1]. The theoretical explanation of the phenomenon put forward in our paper [2] was based on the causal graphical framework [3]. First, using an insightful example together with a causal graph, we have shown that stabilized weights did not account for the confounding due to previous exposure history in a simple misspecified structural model. As further illustrated in simulations, when MSMs fitted using stabilized weights do not appropriately account for previous exposure history, residual confounding bias might be present. We believe that the approach taken by Taguri nicely complements our own. Indeed, it confirms our explanation by noting that in the pseudo-population created by considering stabilized weights, exposures are not mutually independent; this allows the possibility of residual confounding bias due to previous exposure history. Finally, as Taguri noted, our simulation study focused only on linear MSMs without interactions or higher-order terms. The generalizability of our conclusions to other types of MSMs, particularly those where non-collapsibility is present, needs to be further investigated.

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APPENDIX D

Talbot D, Rossi AM, Bacon SL, Atherton J, Lefebvre G. A Graphical Perspective of Marginal Structural Models when Estimating the Causal Relationships Between Physical Activity, Blood Pressure, and Mortality.

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A Graphical Perspective of Marginal Structural Models when Estimating the Causal Relationships Between Physical Activity, Blood Pressure, and Mortality

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Abstract

Estimating causal effects requires important prior subject-matter knowledge and, sometimes, sophisticated statistical tools. The latter is especially true when targeting the causal effect of a time-varying exposure in a longitudinal study. Marginal structural models (MSMs) are a relatively new class of causal models which effectively deal with the estimation of the effects of time-varying exposures. MSMs have traditionally been embedded in the counterfactual framework to causal inference. In this paper, we use the causal graph framework to enhance the implementation of MSMs. We illustrate our approach using data from a prospective cohort study, the Honolulu Heart Program. These data consist of 8,006 men at baseline for which measurements of physical activity and blood pressure were taken at three time-points. Our study focused on the estimation of the causal effects of physical activity on blood pressure, mortality and major adverse cardiovascular events (MACE), and the causal effects of blood pressure on mortality and MACE. First, causal graphs were built to encompass prior knowledge. Those graphs were then validated and improved utilizing structural equation models. We estimated the aforementioned causal effects using MSMs for repeated measures and marginal structural Cox models and guided the implementation of the models with the causal graphs.

1 Introduction

Estimating the causal effect of a time-varying exposure with standard adjusted regression models can lead to biased estimates if a time-varying confounding covariate is an effect of

previous exposure.[1] Marginal Structural Models (MSMs) effectively deal with this issue by using inverse probability weighting.[2–4] When implementing MSMs, a weight is computed for each individual and consists in the product of the inverse propensities of receiving the observed current treatment given prior variables and treatments. A MSM eliminates confounding if the sequential randomization assumption is satisfied, but identifying an appropriate set of variables used to calculate the weights is challenging in practice.[5]

MSMs have traditionally been embedded in Rubin's counterfactual framework to causal inference,[6] even though causal graphs have previously been used to illustrate the relationships between variables in MSMs analyses.[1,7] In this paper, we propose to further embed MSMs in the graphical framework to enhance the implementation of these models.[8] We illustrate our approach using data from the Honolulu Heart Program (HHP). The main objective of our analyses was to estimate the causal effects of physical activity on blood pressure (BP), mortality and major adverse cardiovascular events (MACE), and the causal effects of BP on mortality and MACE. As a secondary objective, we wished to explore the potential mediating role of BP on the causal effects of physical activity on survival and MACE.

In our companion paper,[9] we found that physical activity reduced SBP and both mortality and MACE risks. We also found that lower SBP and DBP reduced mortality and MACE risks. Together, those results suggest that the effects of physical activity on mortality and MACE are at least partly mediated by SBP. The primary aim of the current paper is two-fold: 1) provide a thorough presentation of the statistical methodology used to obtain these results; 2) compare the results obtained using our graphical approach with those obtained using a naive approach for the selection of the variables in the weight

models. A secondary aim is to show the validity of fitting conditional marginal structural models for repeated measures (MSMRMs) in the context implied by our data.

2 Data

The HHP is a cohort study that followed 8,006 Japanese-American men living on the island of Oahu, Hawaii from 1965 until 1994. The participants were initially recruited between 1965 and 1968 from a listing of selective service registrants. The data collection protocol has been described elsewhere.[11] Our analyses were based on three examinations for which comparable measures of physical activity, and both systolic and diastolic blood pressures (SBP and DBP, respectively) were taken: Exam 1 (1965-1968), Exam 2 (1968-1971) and Exam 4 (1991-1993). For those subjects who did not participate at Exam 4, a fourth examination (Exam 3, 1971-1975) was used to estimate their right censorship times due to lost to follow-up. To simplify the presentation, we denote Exam 1, 2 and 4 as Visit 1, 2 and 3, respectively, throughout.

The variables of main interest were self-reported physical activity (active or inactive), SBP (in mmHg), DBP (in mmHg), survival time (in days since birth) and time before a MACE (in days since birth). The HHP variables that were identified as clinically relevant or as potential confounders, and that were measured in a similar manner at all three visits were selected for the analyses. Those variables, which are all time-varying, are: age (in years), employment status (currently employed or not), body mass index (in kg/m^2), smoking status (current smoker, previous smoker or never smoker) and anti-hypertension medication usage (yes or no). More information about how the variables

were measured is available elsewhere.[9]

2.1 Data treatment

We used age in days as the time-scale for both time-to-event variables (survival and time to MACE) and considered them to be left truncated at the time of Visit 1.[12,13] For individuals whose event was not recorded during the study, the time-to-event was right censored at the elapsed time between birth and either the time of their last examination, if they did not attend Visit 3, or one year after Visit 3 otherwise. Note that for each individual, we do not know the exact amount of time elapsed between Visit 3 and the end of monitoring. However, we know it to be at least one year and at most four years. Based on sensitivity analyses (not presented), we took the time between Visit 3 and end of monitoring to be one year. The time to MACE for individuals who died before experiencing a MACE was considered to be right censored at death time (see Bakoyannis and Touloumi (2012) for a discussion and simulations of this approach).[14]

When SBP and DBP were used as exposure variables in the statistical analyses, we divided each of them in four categories according to a common BP classification scheme: < 120mmHg, $120 - 139$mmHg, $140 - 159$mmHg, and $>=$ 160mmHg, for SBP; and < 80mmHg, $80 - 89$mmHg, $90 - 99$mmHg, and $>= 100$mmHg, for DBP.[15]

3 Building causal graphs

The issue of confounding is particularly challenging in the context of longitudinal data, such as the HHP, where intermediate covariates in the pathway between the exposure and

the outcome can also act as confounding covariates. Using substantive prior knowledge, we began by drawing directed acyclic graphs (DAGs) to represent the causal relationships between the selected variables at all visits (see Section 2).[16] The main objective in building the DAGs was to identify sets of variables that could be used to eliminate confounding.

3.1 Building the initial DAGs

Since the secondary objective of our study was to investigate whether SBP and DBP mediate the effects of physical activity on survival and MACE, we constructed one DAG for the relationships between physical activity, SBP, DBP and time of survival (DAG for survival), and one for the relationships between physical activity, SBP, DBP and time to MACE (DAG for MACE). The inclusion or exclusion of arrows between variables and their directionality were carefully decided based on prior knowledge in the scientific literature.

3.2 Assessing the fit of and improving the initial DAGs

We verified if our proposed DAGs fitted the data well using SEMs. SEMs are statistical models that combine qualitative cause-effect assumptions with data to test causal models and estimate causal relationships. Most current SEM packages assume linear relationships between variables and multivariate normality. We used the `lavaan` package in `R` to fit the SEMs and assessed the goodness-of-fit of our proposed causal models with Bollen-Stine bootstrap.[17–19]

Because the number of available subjects is largest at Visit 1 and smallest at Visit 3, we took full advantage of the available information by sequentially fitting larger

and larger models. We began by fitting SEMs that only involved the relationships between the variables at Visit 1, then we fit SEMs for Visits 1 and 2, and lastly, SEMs for Visits 1, 2 and 3. Moreover, since SBP and DBP are often strongly correlated, we fitted separate SEMs for these variables. Thus, we tested a total of six SEMs (1: SBP Visit 1; 2: DBP Visit 1; 3: SBP Visits 1 and 2; 4: DBP Visits 1 and 2; 5: SBP Visits 1, 2 and 3; 6: DBP Visits 1, 2 and 3).

The two initial DAGs we had proposed did not fit the data well according to the chi-square statistics from the six SEMs. This chi-square statistic tests whether the observed data could be compatible with the proposed DAG by comparing the observed covariance matrix of the variables in the SEM with the covariance matrix that is generated by the SEM. Because the fits of the SEMs were poor, we included additional causal links (cause-effect paths and unobserved common causes) between the variables. These links made sense from a substantive point of view and were found using modification indices.

The final SEMs for Visit 1 and the final SEMs for Visits 1 and 2 had non-significant chi-square statistics ($p > 0.05$). Despite the modifications we made, the final SEMs for Visits 1, 2 and 3 still had significant chi-square statistics. We could find no further modifications to the SEMs that made sense from a theoretical point of view. However, we found some observations that were highly influential in the calculations of chi-square statistics. Fitting the models on the data without 69 such observations (2% of the total data) yielded non-significant chi-square statistics. Hence, our SEMs appeared to be reasonable representations of the causal process between the selected variables for most of the data. Using the six final SEMs, we updated our two initial DAGs. Figure 1 presents a part of the final DAG for survival, showing nodes at Visit 1 only. The nodes for SBP and

DBP have been joined into a single BP node in Figure 1 to simplify the presentation. The complete final DAG for the aforementioned relationships is detailed in Rossi et al. (2014).[9] The complete final DAG for MACE is exactly the same as the complete final DAG for survival, except for the time of survival node that is replaced by a time to MACE node.

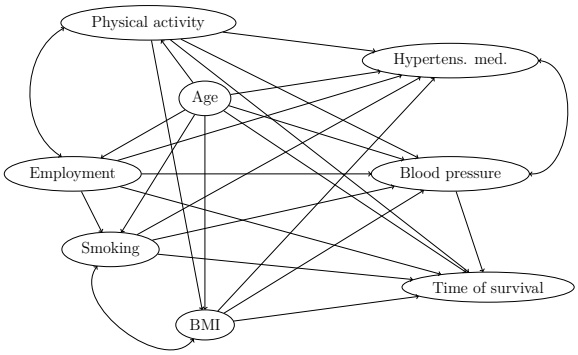

Figure 1: A close-up of the final DAG for time of survival at Visit 1.

3.3 Identifying confounding variables

If a time-varying confounding variable is on the causal pathway between the exposure and the outcome, direct adjustment for this confounding variable in an outcome model could lead to biased estimates.[1] The two complete final DAGs obtained in the previous section confirmed that we were in the presence of such time-varying confounding variables.

On the basis of a causal DAG, Pearl's back-door criterion provides sufficient conditions to identify sets of variables that eliminate confounding when estimating the causal effect of an exposure variable on an outcome variable.[8] In the next two sections, we present the MSMs we used to estimate the causal effects of interest. As subsequently detailed, Pearl's back-door criterion was invoked to identify sets of covariates sufficient to

satisfy the sequential randomization assumption underlying each MSM analysis.

4 Marginal structural models for repeated measures

In this section, we describe the MSMRMs used to estimate the causal effects of physical activity on current SBP and DBP. In the sequel, we generically explain the modeling process in terms of BP, since it is the same for both SBP and DBP. To simplify the presentation, we proceed for now as if all subjects were observed at every visit.

We first introduce some notation for MSMs. Our notation is very similar to that in Hernán et al. (2002),[3] but eliminates the reference to counterfactual outcomes to accommodate the causal graphical framework we consider. Let $i = 1, ..., n$ denote the individuals, $Y(t)$ be the random variable representing the BP value at Visit $t = 1, 2, 3$, and $X(t)$ be the random variable representing the physical activity level at Visit t ($X(t) = 1$ denotes physically active, whereas $X(t) = 0$ denotes physically inactive). We modeled the effect of current and prior physical activity history on current BP as a function of current physical activity (recall the long delay between Visit 2 and Visit 3). We thus considered the following model:

$$E[Y(t)] = \beta_0 + \beta_1 X(t) + \beta_2 Age(t), \tag{1}$$

where β_0 is the unknown intercept, β_1 is the unknown parameter associated with the physical activity level and β_2 is the unknown slope parameter associated with the age of subjects at Visit t. Note that it is common in MSMRMs to introduce a parameter associated with t, the Visit number, to allow the intercept to vary with time.[3] Because we

have considered age as being the time-scale for both survival and time to MACE, it was natural to instead consider a parameter associated with age.

Ignoring the complications arising from missing data and possible informative censoring, the parameters of model (1) can be directly estimated by fitting a GEE regression to an augmented dataset, where each line corresponds to a given subject at a given visit. However, for β_1 to have a causal interpretation, time-varying confounding must be adequately dealt with. This is done by attributing an inverse probability of treatment weight (IPTW) to each subject-visit.

As seen next in Equation (3), sets of variables $\boldsymbol{L}^{XY}(t)$, $t = 1, 2, 3$, were used to calculate the subject-specific IPTWs. Let $y_i(t)$, $x_i(t)$ and $\boldsymbol{l}_i^{XY}(t)$ be the respective observed realizations of $Y(t)$, $X(t)$ and $\boldsymbol{L}^{XY}(t)$ for subject i. In the counterfactual framework, the variables $\boldsymbol{L}^{XY}$ entering the weight models are chosen so that the sequential (conditional) randomization assumption holds.[3] Because of how model (1) is specified, this assumption can be simplified as:

$$Y_{\bar{x}}(t) \perp\!\!\!\perp X(t) | \boldsymbol{L}^{XY}(t), \quad \forall\, \bar{x}, t \in \{1, 2, 3\}, \tag{2}$$

where $Y_{\bar{x}}(t)$ is the counterfactual BP value at Visit t that would have been observed if, possibly contrary to the fact, the physical activity history $\bar{x}$ had been observed. Considering Theorem 4.4.1 from Pearl (2009),[8] Section 4.4.3, we find that the effect of $X(t)$ on $Y(t)$ can be identified conditional on $\boldsymbol{L}^{XY}(t)$ if $\boldsymbol{L}^{XY}(t)$ is a set of non-descendants of $X(t)$ that blocks every back-door path from $X(t)$ to $Y(t)$. Hence, on the basis of the complete final DAGs mentioned in Section 3, we selected the variables in $\boldsymbol{L}^{XY}(t)$ to

satisfy the back-door criterion. A complete list of the variables in $\boldsymbol{L}^{XY}$ is available in eAppendix A.

We considered the weighted GEE regression model (1) with stabilized weights

$$W_i^{XY}(t) = \prod_{k \leq t, k \in \{1,2,3\}} \frac{P(X(k) = x_i(k))}{P(X(k) = x_i(k) | \boldsymbol{L}^{XY}(k) = \boldsymbol{l}_i^{XY}(k))} \tag{3}$$

and estimated $P(X(k) = x_i(k))$ and $P(X(k) = x_i(k) | \boldsymbol{L}^{XY}(k) = \boldsymbol{l}_i^{XY}(k))$ using logistic regression.[20]

4.1 Estimation with incomplete data

Up until now, we have presented the MSMRMs we would have fitted to estimate the effect of physical activity on BP had there been no deaths or losses to follow-up. Recall that the HHP is a longitudinal study that spanned over a very long period of time. Inevitably, many subjects died before the end of the study or were lost to follow-up. Therefore, we did not have a complete dataset where every subject participated at every visit. Because a weighting scheme is already used to account for confounding, we used inverse probability of censoring weights (IPCWs) to deal with incomplete follow-up in our MSMRMs.[3,21]

Let $C(t)$ be a random variable representing the censoring at Visit t, with $C(0) \equiv 0$, and let $c_i(t)$ be the observed realization for subject i ($c_i(t) = 0$ if subject i is still in the study at Visit t and $c_i(t) = 1$ otherwise). Also, let $\boldsymbol{Z}(t)$ denote the covariates available at Visit t and $\boldsymbol{z}_i(t)$ be their observed values for subject i. Our weights for censoring are

$$W_i^{C}(t) = \prod_{k \leq t, k \in \{1,2,3\}} \frac{P(C(k) = 0 | C(k-1) = 0)}{P(C(k) = 0 | C(k-1) = 0, \boldsymbol{Z}(k) = \boldsymbol{z}_i(k))}.$$

We estimated $P(C(k)=0|C(k-1)=0)$ and $P(C(k)=0|C(k-1)=0, \boldsymbol{Z}(k)=\boldsymbol{z}_i(k))$ using logistic regression. For $i = 1, ..., n$, we computed the total weights as $W_i^{Total}(t) = W_i^C(t) \times W_i^{XY}(t)$, and then calculated the corresponding normalized weights $NW_i^{Total}(t)$ as described in Equation (4) in Xiao et al. (2014).[4] Finally, the GEE regression (1) was fitted with weights $NW_i^{Total}(t)$. We used an independent working correlation matrix and a robust variance estimator to account for the repeated measures in the GEE regression.[22,23]

4.2 Conditional marginal structural models for repeated measures

It is usually recommended not to include time-varying variables in the outcome model (1) of a MSMRM.[3] This is because some of these variables can act both as confounders and intermediate variables over time.[1] In this section, we argue that it is safe to include time-varying variables $\boldsymbol{U}(t)$ in the model we consider, even if $\boldsymbol{U}(t)$ includes such time-dependent confounders.

We also considered the following conditional model to estimate the causal effect of physical activity on BP:

$$E[Y(t)|\boldsymbol{U}(t)] = \beta_0 + \beta_1 X(t) + \beta_2 Age(t) + \boldsymbol{\beta}_3 \boldsymbol{U}(t), \tag{4}$$

where $\boldsymbol{\beta}_3$ is a vector of unknown parameters. With the back-door criterion in mind, the variables $\boldsymbol{U}(t)$ we selected were such that they were not descendants of $X(t)$ according to our complete final DAGs. These variables are *Employment* and *Smoking* at Visit t. Note that $\boldsymbol{U}(t)$ may have included variables on the causal pathway between $X(s)$ and $Y(t)$,

$s < t$, without introducing bias in the estimation of β_1. This is because model (4) only considers the effect of $X(t)$ on $Y(t)$.

We estimated the corresponding causal effect of physical activity on BP as presented in Section 4.1. That is, we built an augmented dataset and fitted the weighted GEE regression model (4) using the same normalized weights as before. In the sequel, we refer to model (4) we have just introduced as a conditional MSMRM, as opposed to the unconditional MSMRM presented previously. In eAppendix B, we present a simulation study that validates our methodology.

5 Marginal structural Cox models

We used MSCMs to estimate the causal effects that involved the two time-to-event outcomes of interest, that is, survival time and time to MACE. We describe in detail the process we followed for the estimation of the causal effect of physical activity on survival time. The estimation process for each of the three other relationships investigated was similar (additional precisions are provided at the end of this section). Our MSCM methodology has strong connections with the one proposed by Xiao et al. (2010).[4] It also shares similarities with the MSMRM methodology described in the previous section.

We believe that the causal effect of physical activity history on survival time is mostly a function of current physical activity level. Hence, we considered the following model for the hazard at age τ

$$\lambda(\tau) = \lambda_0(\tau) \exp(\beta_1 X(\tau)), \tag{5}$$

β_1 is the unknown parameter associated to the physical activity level $X(\tau)$ and $\lambda_0(\tau)$ is the unspecified baseline hazard at age τ. Because physical activity was only measured at the ages corresponding to examinations, we took $X(\tau)$ as a step function with steps at the ages corresponding to examinations. Once again, the time-varying confounding problem is solved by using inverse probability weighting.

We define $\boldsymbol{L}^{XT}(t)$ and $W_i^{XT}(t)$ analogously to $\boldsymbol{L}^{XY}(t)$ and $W_i^{XY}(t)$ (see Equation (3)), only replacing BP (Y) by survival time (T). To satisfy the conditional ignorability assumption of the MSCMs,[2] we selected the variables $\boldsymbol{L}^{XT}(t)$ on the basis of the complete final DAG for survival and the back-door criterion. The list of the selected variables is again provided in eAppendix A.

We normalized the weights $W_i^{XT}(t)$ as in Equation (4) from Xiao et al. (2010) and fitted a weighted Cox model with hazard (5) utilizing those normalized weights.[4] We used a robust estimator for the estimation of the standard errors.

We used exactly the same approach to estimate the causal effect of physical activity on time to MACE, only replacing survival time by time to MACE. Moreover, only minor changes to the methodology were done to estimate the causal effects of SBP and DBP on survival time and on time to MACE. As mentioned in Section 2.1, we divided the SBP and DBP values into four categories when these BP variables were used as exposure variables. The probabilities $P(X(k) = x_i(k))$ and $P(X(k) = x_i(k)|\boldsymbol{L}^{XT}(k) = \boldsymbol{l}_i^{XT}(k))$ required in the calculation of $W_i^{XT}(t)$ were estimated using ordinal logistic regression models.

6 Contrasting our approach with a naive approach

We have presented in the previous sections a graphical approach to MSMs where the covariates selected for estimating the IPTWs are identified using DAGs and the back-door criterion. A more naive approach for estimating the IPTWs is to use every potentially confounding covariates available at a given visit.

The first line of Table 1 presents the results obtained by estimating the causal effects of physical activity on SBP and DBP using the unconditional MSMRM described in Section 4. For the naive approach, the causal effects were estimated similarly, only replacing $\boldsymbol{L}^{XY}(t)$ by $\boldsymbol{L}_N^{XY}(t)$ in the IPTWs (3). The variables in $\boldsymbol{L}_N^{XY}(t)$, $t = 1, 2, 3$, are listed in eAppendix A. The results obtained using the naive approach are presented in the second line of Table 1.

The estimated causal effects of physical activity on SBP obtained with the naive and the graphical approaches are both compatible with a decrease in SBP when physically active. However, the interpretation of the results for DBP differs. Indeed, the results obtained using the graphical approach are compatible with no effect of physical activity on DBP, whereas the results pertaining to the naive approach suggest that being physically active *increases* DBP. That physical activity would increase DBP is not supported by the current scientific knowledge.[24] The observed divergence in conclusions lends support to our proposed approach.

Table 1: Results from the graphical and naive approaches to estimate the causal effect of current physical activity on SBP and DBP (95% confidence intervals in parenthesis).

Approach	SBP	DBP
Graphical	-2.47 (-3.46, -1.48)	0.26 (-0.22, 0.75)
Naive	-1.64 (-2.64, -0.64)	0.96 (0.47, 1.44)

7 Comparing conditional and unconditional MSMRMs

Conditional MSMRM estimates of the effects of physical activity on SBP and DBP are not reported in our companion paper. A first step was to perform a simulation study to investigate the validity of a conditional version of the MSMRMs (see eAppendix B). A comparison of the estimates obtained using the unconditional MSMRM (1) and the conditional MSMRM (4) is presented in Table 2. The conditional MSMRM involves the time-varying covariates $\boldsymbol{U}(t) = \{$*Employment* and *Smoking* at Visit $t\}$. The results obtained using conditional and unconditional MSMRMs are consistent, although a reduction of more than 1 mmHg in SBP is observed for the conditional effect. No clear benefit was seen with the use of a conditional MSMRM for this application. However, the simulation results suggest that conditional MSMRM yields unbiased and more precise estimates in some situations.

Table 2: Results from using unconditional and conditional MSMRMs to estimate the causal effects of physical activity on SBP and DBP (95% confidence intervals in parenthesis). Note that only the parameter associated with physical activity has a causal interpretation.

Parameter	Unconditional SBP	Conditional SBP
Physical activity	**-2.47 (-3.46, -1.48)**	**-1.33 (-2.28, -0.38)**
Age	0.70 (0.61, 0.78)	0.44 (0.36, 0.52)
Employed	NA	-12.71 (-13.65, -11.78)
Current smoker	NA	-1.14 (-2.15, -0.14)
Previous smoker	NA	1.69 (0.65, 2.74)

Parameter	Unconditional DBP	Conditional DBP
Physical activity	**0.26 (-0.22, 0.75)**	**0.16 (-0.33, 0.65)**
Age	-0.07 (-0.11, -0.03)	-0.04 (-0.09, 0.00)
Employed	NA	1.72 (1.24, 2.20)
Current smoker	NA	-1.79 (-2.34, -1.25)
Previous smoker	NA	-0.23 (-0.79, 0.33)

8 Discussion

Using the HHP to illustrate our approach, we have devised and implemented MSMs in the graphical framework to causal inference. This graphical framework can be particularly helpful when selecting variables used to construct the IPTWs, which are central to fitting MSMs to data. Selecting variables to calculate IPTWs has previously been recognized as a challenge in the implementation of MSMs.[5] This was further illustrated in Section 6 of our paper, where a naive approach to variable selection was shown to yield implausible results.

Contrariwise, the graphical approach we have developed for the analysis of the HHP data gave results more consistent with current scientific knowledge.

We have also proposed a conditional version of the MSMRMs to estimate the causal effects of physical activity on SBP and DBP. Although no clear advantages were seen for the HHP data, the use of conditional MSMRMs ought not to be neglected in practice. Indeed, the simulation we performed resulted in unbiased conditional estimators with smaller standard errors than the unconditional ones. It is important to keep in mind that conditional MSMRMs were fitted in a very specific context in which the physical activity history was summarized using only the most recent level of physical activity. However, our approach could easily be generalized to other situations, for instance where physical activity history is summarized using the two most recent levels of physical activity.

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A Variables used in IPTWs

Here is a list of the variables used in the calculations of the IPTWs.

- To estimate the causal effects of physical activity on SBP or DBP ($\boldsymbol{L}^{XY}$), and survival or MACE ($\boldsymbol{L}^{XT}$) :
  - $\boldsymbol{L}^{XY}/\boldsymbol{L}^{XT}(1) = \{$age at Visit 1, employment at Visit 1$\}$
  - $\boldsymbol{L}^{XY}/\boldsymbol{L}^{XT}(2) = \{$age at Visit 2, BMI at Visit 1, employment at Visit 2, hypertension medication usage at Visit 1, physical activity level at Visit 1$\}$
  - $\boldsymbol{L}^{XY}/\boldsymbol{L}^{XT}(3) = \{$age at Visit 3, BMI at Visit 2, employment at Visit 3, hypertension medication usage at Visits 1 and 2, physical activity level at Visits 1 and 2$\}$
- To estimate the causal effects of SBP on time of survival and time to MACE :
  - $\boldsymbol{L}^{XT}(1) = \{$age at Visit 1, BMI at Visit 1, employment at Visit 1, physical activity level at Visit 1$\}$
  - $\boldsymbol{L}^{XT}(2) = \{$age at Visit 2, BMI at Visits 1 and 2, employment at Visit 2, hypertension medication usage at Visit 1, physical activity level at Visits 1 and 2, SBP at Visit 1$\}$
  - $\boldsymbol{L}^{XT}(3) = \{$age at Visit 3; BMI at Visits 1, 2 and 3; employment at Visit 3; hypertension medication usage at Visits 1 and 2; physical activity level at Visits 1, 2 and 3; SBP at Visits 1 and 2$\}$

- The weights used for estimating the causal effects of DBP on time of survival and time to MACE were analogous to the preceding ones, only replacing SBP by DBP.

- The variables used for computing the naive weights, $\boldsymbol{L}_N^{XY}(t)$, $t = 1, 2, 3$, in Section 6 for estimating the causal effects of physical activity on SBP and DBP :

  - $\boldsymbol{L}_N^{XY}(1)$ = {age at Visit 1, BMI at Visit 1, employment at Visit 1, hypertension medication usage at Visit 1 and smoking at Visit 1}

  - $\boldsymbol{L}_N^{XY}(2)$ = {age at visit 2, BMI at Visits 1 and 2, employment at Visits 1 and 2, hypertension medication usage at Visits 1 and 2, smoking at Visits 1 and 2, physical activity level at Visit 1, SBP at Visit 1, DBP at Visit 1}

  - $\boldsymbol{L}_N^{XY}(3)$ = {age at visit 3; BMI at Visits 1, 2 and 3; employment at Visits 1, 2 and 3; hypertension medication usage at Visits 1, 2 and 3; smoking at Visits 1, 2 and 3; physical activity level at Visits 1 and 2; SBP at Visits 1 and 2; and DBP at Visist 1 and 2}

B Simulation study for the conditional MSMRM

All the simulation scenarios are compatible with the DAG depicted in Figure 2; the exact data-generating equations however differ slightly between scenarios. Although this DAG is simple, it is sufficient to illustrate the main properties of our conditional MSMRM approach.

Scenario 1 is (essentially) the same as Scenario 3 in Talbot et al. (2014).[20] The equations that generated the data are:

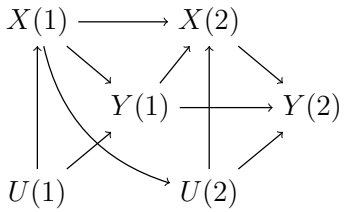

Figure 2: DAG for Scenarios 1-4

$$U(1) = \varepsilon_{U(1)},$$

$$P(X(1) = 1) = expit(0.5U(1)),$$

$$Y(1) = X(1) + U(1) + \varepsilon_{Y(1)},$$

$$U(2) = 0.5X(1) + \varepsilon_{U(2)},$$

$$P(X(2) = 1) = expit(0.5X(1) + 0.5Y(1) + 0.5U(2)),$$

$$Y(2) = X(2) + 0.5Y(1) + U(2) + \varepsilon_{Y(2)},$$

where $expit(z) = exp(z)/(1 + exp(z))$, and $\varepsilon_{U(1)}$, $\varepsilon_{Y(1)}$, $\varepsilon_{U(2)}$, $\varepsilon_{Y(2)}$ are independent $N(0, 1)$ random variables.

Scenario 2 is the same as Scenario 1, but replaces the strong links from $U(1)$ to $Y(1)$, and from $U(2)$ to $Y(2)$ with weak links:

$$Y(1) = X(1) + 0.1U(1) + \varepsilon_{Y(1)}, \text{ and}$$

$$Y(2) = X(1) + 0.5Y(1) + 0.1U(2) + \varepsilon_{Y(2)}.$$

All other data-generating equations are the same as in Scenario 1.

Scenario 3 is also the same as Scenario 1, but features an even stronger link from $U(1)$ to $Y(1)$, and from $U(2)$ to $Y(2)$:

$$Y(1) = X(1) + 2U(1) + \varepsilon_{Y(1)}, \text{ and}$$
$$Y(2) = X(1) + 0.5Y(1) + 2U(2) + \varepsilon_{Y(2)}.$$

Scenario 4 is very similar to Scenario 1, but presents an *interaction* between $U(1)$ and $X(1)$, and between $U(2)$ and $X(2)$. Before introducing Scenario 4, we first define $U^*(2)$ as a centered (to 0) version of $U(2)$. This centering is done for convenience and to ensure that the marginal total effect of $X(2)$ on $Y(2)$ equals 1. Also, remark that the marginal total effect of $X(1)$ on $Y(1)$ equals 1. The data-generating equations for Scenario 4 that differ from Scenario 1 are:

$$Y(1) = X(1) + U(1) + X(1) \times U(1) + \varepsilon_{Y(1)}, \text{ and}$$
$$Y(2) = X(2) + 0.5Y(1) + U^*(2) + X(2) \times U^*(2) + \varepsilon_{Y(2)}.$$

For each simulation scenario, we generated 10,000 datasets of size $n = 500$. For each dataset, we estimated the causal effect of $X(t)$ on $Y(t)$, $t = 1, 2$, using the estimated parameter associated to $X(t)$, namely $\hat{\beta}_1$, in 1) an unweighted GEE regression (crude analysis), 2) an unconditional MSMRM, and 3) a conditional MSMRM. The true causal

effect equals 1 for each scenario. We computed the mean and the standard deviation of $\hat{\beta}_1$ across generated datasets for each method. The outcome models fitted in the unconditional and conditional MSMRMs analyses were the same for all simulation scenarios, and were respectively:

$$E(Y(t)) = \beta_0 + \beta_1 X(t) + \beta_2 t, \text{ and}$$

$$E(Y(t)|U(t)) = \beta_0 + \beta_1 X(t) + \beta_2 t + \beta_3 U(t).$$

Note that even though the true structural equations of Scenario 4 involve interaction terms and a centered version of $U(2)$, the fitted structural model does not. The fitted model is therefore misspecified.

Each subject-visit was attributed a normalized version of the following weights:

$$\begin{aligned} W_i^{XY}(1) =& \frac{P(X(1) = x_i(1))}{P(X(1) = x_i(1)|U(1) = u_i(1))}, \text{ and} \\ W_i^{XY}(2) =& \frac{P(X(1) = x_i(1))}{P(X(1) = x_i(1)|U(1) = u_i(1))} \\ & \times \frac{P(X(2) = x_i(2))}{P(X(2) = x_i(2)|U(1) = u_i(1), Y(1) = y_i(1), U(2) = u_i(2))}, \end{aligned}$$

where the normalization was performed as in Equation (4) from Xiao et al. (2010).[4] Those weights were used to fit both the conditional and unconditional MSMSRMs.
The specification of the crude GEE regression was the same as the specification of the unconditional MSMRM, but with $W_i^{XY}(1) \equiv W_i^{XY}(2) \equiv 1$.

The results of the simulation study are presented in Table 3. Those results confirm that the conditional MSMRM (4) can yield unbiased estimates of β_1 if the weights are correctly specified and if $\boldsymbol{U}(t)$ does not include descendants of $X(t)$. The results for Scenario 4 support that this conclusion holds even when there are interactions between some variables in $\boldsymbol{U}(t)$ and $X(t)$. Moreover, the conditional MSMRM is often more efficient than the unconditional MSMRM when estimating β_1. In fact, the results for Scenarios 1, 2 and 3 suggest that the more $\boldsymbol{U}(t)$ predicts $Y(t)$, the greater is the reduction in the variance of $\hat{\beta}_1$.

Table 3: Results from simulation Scenarios 1-4 obtained by generating 10,000 datasets of size $n = 500$. The mean and the standard deviation (in parenthesis) of $\hat{\beta}_1$ are provided. The true causal effect is 1.

Model	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Crude	1.808 (0.103)	1.223 (0.074)	2.558 (0.161)	2.138 (0.129)
Unconditional MSMRM	1.001 (0.087)	1.000 (0.074)	1.009 (0.149)	1.006 (0.114)
Conditional MSMRM	1.000 (0.077)	1.000 (0.074)	1.005 (0.100)	1.003 (0.092)

APPENDIX E

Rossi AM, Bacon SL, Moullec G, Gour-Provençal G, Lavoie KL. The evolution of a Canadian Hypertension Education Program recommendation: the impact of resistance training on resting blood pressure in adults as an example. *Canadian Journal of Cardiology*. 2013; 29(5):622-7

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Systematic Review/Meta-analysis

The Evolution of a Canadian Hypertension Education Program Recommendation: The Impact of Resistance Training on Resting Blood Pressure in Adults as an Example

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ABSTRACT

Ever since the first set of hypertension recommendations which were generated from the Canadian Hypertension Education Program, lifestyle and health behaviour have been a key focus. An initial recommendation focused on the benefits of aerobic exercise to reduce resting blood pressure (BP). However, until the 2013 edition, resistance exercise (RT) was not included. The current article describes a meta-analysis that was conducted which helped inform the creation of the newly introduced recommendation. Literature searches were conducted in 4 electronic databases. Inclusion criteria included: (1) randomized controlled trials with 4-week minimum, RT-alone intervention arms; (2) BP-lowering as the primary outcome; (3) human, adult participants; and (4) reporting control data, baseline, and post-intervention resting systolic BP and diastolic BP. Nine studies (11 intervention groups, 452 participants) were identified. The analyses indicated that diastolic BP was significantly reduced (−2.2 mm Hg; 95% confidence interval, −3.9 to −0.5) in those randomized to RT compared with control participants. In contrast, no statistically significant change in systolic BP (−1.0 mm Hg; 95% confidence interval, −3.4 to 1.4) was observed. None of the studies found RT to increase BP and no adverse effects of RT were explicitly reported. Results suggest that participation in RT is not harmful and does not increase BP. However, more evidence is needed before recommending RT as a specific BP-lowering therapy.

RÉSUMÉ

Depuis la première série de recommandations sur l'hypertension qui avaient été formulées par le Programme éducatif canadien sur l'hypertension, le style de vie et le comportement lié à la santé ont été les principales préoccupations. Une recommandation initiale a mis l'accent sur les avantages de l'exercice aérobique pour réduire la pression artérielle (PA) au repos. Cependant, jusqu'à l'édition 2013, entraînement musculaire (EM) n'avait pas été inclus. Le présent article décrit une méta-analyse qui avait été menée et qui a permis d'appuyer la création de la nouvelle recommandation. Les recherches bibliographiques ont été menées à partir de 4 bases de données électroniques. Les critères d'inclusion ont inclus : 1) les essais aléatoires d'un minimum de 4 semaines, les bras d'intervention par l'EM seul; 2) la diminution de la PA comme critère de jugement primaire; 3) des participants humains adultes; 4) la communication des données de PA systolique et de PA diastolique de témoins au repos au début et après l'intervention. Neuf (9) études (11 groupes d'intervention, 452 participants) ont été identifiées. Les analyses ont indiqué que la PA diastolique avait été significativement réduite (−2,2 mm Hg; intervalle de confiance à 95 %, −3,9 à −0,5) chez ceux répartis au hasard à l'EM comparativement aux participants témoins. Par opposition, aucun changement statistiquement significatif de la PA systolique (−1,0 mm Hg; intervalle de confiance à 95 %, −3,4 à 1,4) n'avait été observé. Aucune étude n'a montré que l'EM augmentait la PA et aucun effet indésirable de l'EM n'a été explicitement rapporté. Les résultats suggèrent que l'EM n'est pas mauvais et qu'il n'augmente pas la PA. Cependant, davantage de données scientifiques sont nécessaires avant de recommander l'EM comme thérapie pour abaisser la PA.

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See page 626 for disclosure information.

Though the initial report from the Canadian Consensus Conference on Nonpharmacologic Approaches to the Management of High Blood Pressure in 1989 suggested that there was positive, but inconclusive benefits for aerobic exercise for lowering blood pressure (BP),[1] the subsequent consensus

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statement from 1999 provided Canada with its first explicit exercise recommendations.[2] That recommendation was focused on the utility of aerobic exercise to reduce blood pressure in those at risk for and those with hypertension and formed the basis for all subsequent iterations of the Canadian Hypertension Education Program (CHEP) recommendations.[3] Though research during the past 10 years or so has strengthened and improved on the data linking aerobic exercise with reduced BP there has been a growing literature assessing the effect of resistance exercise (RT) interventions and training on BP.

In the context of recommendation generation, the American College of Sports Medicine (ACSM), in its 2004 Position Stand on Exercise and Hypertension, was the first organization to provide a specific recommendation for the use of dynamic RT to reduce BP.[4] Other organizations have been more cautious with regard to the potential benefits of RT, for example, the American Heart Association and the European Society of Cardiology comment on the use of RT to lower or control BP but neither provide a specific recommendation.[5,6] In subsequent American Heart Association guidelines on resistant hypertension,[7] hypertension in patients with ischemic heart disease,[8] and hypertension in the elderly,[9] and European Society of Cardiology guidelines on cardiovascular disease prevention[10] the benefits of aerobic exercise for lower BP are detailed, but there is no mention of RT.

To date the best evidence available on the effect of RT on BP has come from a recent meta-analysis by Cornelissen et al.[11] (which was published after most of the guidelines and statements noted above). This meta-analysis found that RT interventions have a BP-lowering effect in normotensive or prehypertensive individuals (systolic BP [SBP] change, −3.9 [95% confidence interval (CI), −6.4 to −1.2] mm Hg and diastolic BP [DBP] change, −3.9 [95% CI, −5.6 to −2.2] mm Hg), but not in individuals with hypertension. However, several methodologicaldetails of this meta-analysis are important to note.[12] Specifically, the study included trials that did not focus on BP as a primary end point. In the context of how CHEP evaluates evidence, this is considered important because the inclusion of studies in which BP is not the primary end point are more likely to be subject to outcome reporting biases which can influence effect estimates.[13-15] In addition, the inclusion of isometric handgrip exercise might be limiting from a practical standpoint. Though there is some limited evidence that these exercises might reduce BP,[16] only dynamic RT has been shown to improve non-BP health-related proxies and outcomes (eg, maintenance of lean muscle mass and bone mineral density, and improved glycemic control in diabetic patients).[17-19] As such, from a public health context it is important to specifically evaluate the effect of dynamic RT on BP, which is consistent with the ACSMs position statement.[20]

The goal of the meta-analyses detailed below was to provide the CHEP health behaviours subcommittee with complementary evidence to that of Cornelissen et al.,[11] which fit with CHEP's conceptual framework (ie, the inclusion of only studies that used BP as a primary outcome measure). As with the Cornelissen report,[11] a series of secondary analyses were conducted to assess factors which might influence the RT-BP relationship. However, these were extended to include an analysis of sex differences because non-RT exercise differences in men vs women have been previously documented.[21]

Methods

Literature search and study selection

A comprehensive literature search of English-language, peer-reviewed articles was conducted with the MedLine, Embase, SportsDiscus, and Cochrane Library electronic databases from their respective inception dates through November 2012 (see Supplemental Table S1 for the search strategy). Relevant articles identified within reference lists were also considered. The inclusion criteria for studies were: (1) randomized controlled trials (RCTs) with 4-week minimum, RT-alone intervention arms (excluding handgrip/isometric exercises); (2) BP-lowering was the primary outcome; (3) human studies with adult (> 18 years of age) participants; and (4) studies reported control data, baseline, and postintervention resting SBP and DBP. The flow diagram in Figure 1 represents the process of record elimination. Eligible records were independently reviewed by 2 authors (A.M.R., G.G.P.) and any discrepancies were settled through a consensus discussion.

Data extraction and risk of bias assessment

Coding forms containing 304 items with information on patient characteristics, intervention description, outcome data, and attendance and compliance were created using Microsoft Access 2007. To reduce bias, all data were independently entered by 2 authors (A.M.R., G.G.P.) and compared using SAS v9.2, after which the authors met to rectify disagreements. Details of the risk of bias assessments can be found in the *Methods* section Supplementary Material.

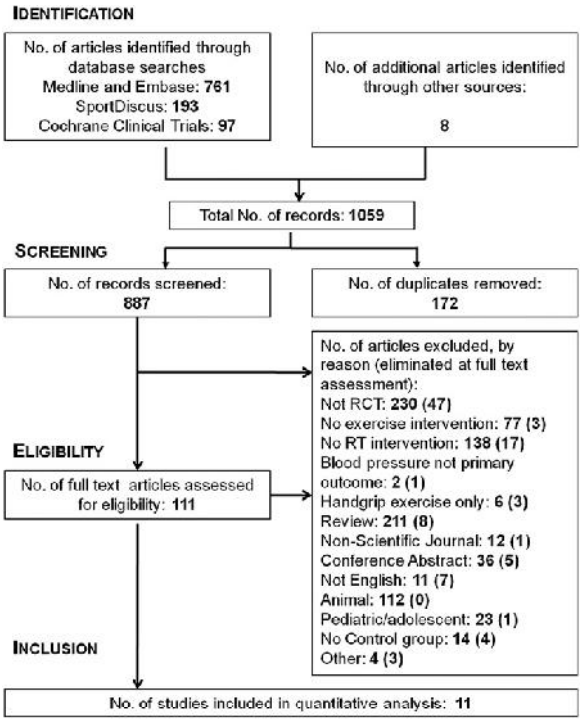

Figure 1. Search procedure and elimination scheme. RCT, randomized controlled trial; RT, resistance training.

Statistical analysis

Trial results were pooled by calculating weighted mean differences and 95% CI for each effect (2-tailed) in Review Manager version 5.0.25 (Cochrane Collaboration, Oxford, UK). The primary outcome measure was the net changes in SBP and DBP (treated separately). The secondary outcomes were net changes in heart rate and peak oxygen uptake (VO_2max), which are reported in Supplemental Table S3. Net changes were calculated as the mean difference (RT values minus control values) of the change (follow-up values minus baseline values) in BP and were calculated for each intervention group. If mean changes and standard deviation (SD) from baseline were not reported, the unadjusted pre- and post differences and corresponding SD were calculated using previously suggested methods.[22] Additional analyses to assess the potential effect of covariates on net BP changes are included in Supplemental Table S3. To identify possible publication bias, we performed funnel-plots of net changes in SBP and DBP. We measured the inconsistency of effects between study findings using the I^2 statistic as proposed by Higgins et al. (ie, percentage of total variation across studies because of heterogeneity rather than chance).[23] According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, if random and fixed effect models produced the same results, only the results from fixed effect models should be presented,[24] which was the case in the present study. When heterogeneity was high (> 50%) and could not be explained by clinical or methodological factors, we used a random effect model.[25]

Results

Studies included

Figure 1 displays a flow diagram which summarizes the study selection and inclusion process. The searches yielded 887 citations (after removing duplicates). As of November 2012, a total of 11 articles including 14 intervention groups, met all inclusion criteria.[26-36] None of the studies indicated whether the data were analyzed according to the number of participants who completed the trial or using data from all participants after randomization allocation (ie, intention to treat), which is a general limitation of the existing literature.

Study characteristics

Participant characteristics. Baseline participant characteristics and study design information can be found in Supplemental Table S2. The selected studies were published between 1987 and 2012. A total of 452 participants were included in the analysis. Five studies included men only[29,31,32,35,36] and only 1 study examined the effects of RT in women only.[30] The study samples consisted of adults ranging from 19 to 74 years of age (mean, 49 years; median, 50 years) with sample sizes ranging from 16 to 132 participants (mean, 20; median, 13). Three studies were conducted with hypertensive patients.[26,27,29] In the report by Blumenthal et al.,[26] the participants were withdrawn from medication before engaging in the exercise program. Cononie et al.[27] indicated that only 4 of 11 participants were taking medication, and both reported no change in medications during the trail. Although Harris and Holly[29] classified participants as borderline hypertensive (SBP = 140-160 mm Hg; DBP = 90-95 mm Hg) they did not describe medication usage in their sample. One study specifically evaluated asymptomatic, controlled, type II diabetic patients.[28] The remaining studies consisted of normotensive participants.[30-36]

Intervention characteristics. Information about the nature of the RT interventions can be seen in Supplemental Table S2. Overall, reporting of the details of the RT interventions was poor. The intervention duration ranged from 6 to 24 weeks (mean, 14.6 weeks; median, 16 weeks). Training frequency was consistently reported to be 3 sessions per week for all intervention protocols. Training intensity varied between 30% and 80% of the participants' 1-repetition maximum (%1RM) (mean, 55% %1RM; median, 50% %1RM). Most exercise programs consisted of combined core (eg, sit-ups) exercise with upper and lower body exercises (eg, biceps curls and squats, respectively), although neither the specific details of the programs nor the total duration of each exercise session were clearly defined in the studies. None of the studies reported on extended, postintervention follow-up assessments. Blood pressure measurement was generally well described. Most reports specified the method of measurement, number of measurements taken, and patient position. Most reports complied with current recommendations for BP measurement,[26-28,30,32,33,35,36] however, in several instances not enough information was available to judge the quality of BP measurement.[29,31,34]

Effect of RT on blood pressure

Pre- and postintervention BP are displayed in Supplemental Table S3. As shown in Figure 2, the analyses indicated that after RT, DBP was significantly reduced by 2.2 mm Hg (95% CI, −3.9 to −0.5) in individuals randomized to RT compared with control participants. A nonsignificant net SBP change of −1.0 mm Hg (95% CI, −3.4 to 1.4) was also observed (see Fig. 3). The I^2 statistic was found to be 61% for SBP and 54% for DBP which indicates there is some heterogeneity between studies. Baseline and post exercise absolute BP per study is reported in Supplemental Table S3.

Study quality and publication bias

Results of the study quality and publication bias can be found in the Supplementary Material (*Results* section; Supplemental Figures S1 and S2).

Discussion

Effect of RT on resting BP levels

The purpose of this meta-analysis was to provide complementary evidence to that which currently exists and improve the precision of the estimated effect of RT on BP. The results indicate that participation in a RT program is associated with a statistically significant reduction in DBP of 2.2 mm Hg but a nonstatistically significant reduction in SBP of 1.0 mm Hg. These results are somewhat inconsistent with the Cornelissen et al. study,[11] which found a significant SBP and DBP decrease of 2.8 and 2.7 mm Hg, respectively, for dynamic RT (with an overall significant reduction of 3.9 and/or

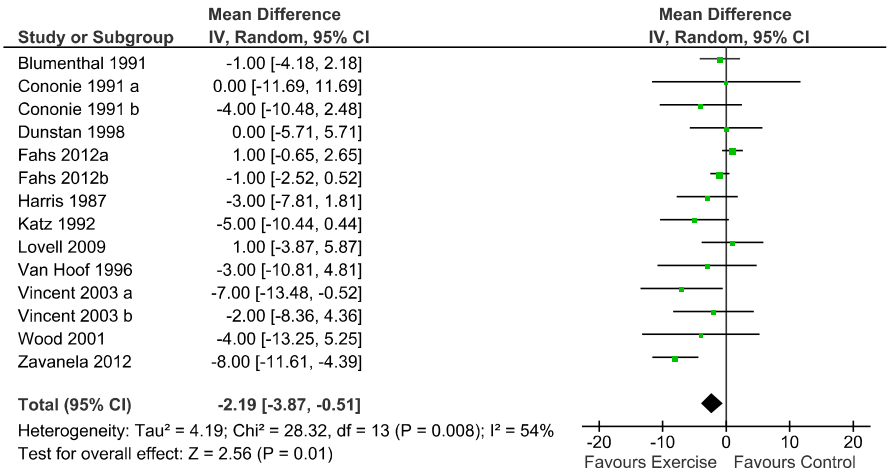

Figure 2. Pooled effect of resistance training on DBP. Average change in DBP and corresponding 95% CI for all 11 resistance training intervention groups in 9 RCTs, of note, the different training groups within an individual study are represented by an a or b. CI, confidence interval; DBP, diastolic blood pressure; df, degrees of freedom; IV, independent variable; RCT, randomized controlled trial.

3.6 for any RT). Of importance, neither meta-analysis found that RT increased SBP or DBP nor did either systematic review identify any single study which found RT to increase BP. Though additional adverse events were not explicitly commented on in all the analyzed studies, there were no studies that reported any severe adverse events related to RT.

As noted, the discrepancy in the SBP finding between the current analysis and the Cornelissen et al.[11] study might be attributed to methodological differences[12] (ie, the inclusion of studies in which BP was not the primary outcome). Even though the inclusion of these studies might be considered more inclusive, it increases the risk of overestimating effect sizes,[13-15] which might be the case here, and is less consistent with the way in which CHEP reviews data. A conservative appraisal of the available data suggests that there is no detrimental effect of RT on BP and that there might be a modest improvement in DBP but no improvement in SBP. Considering that dynamic RT has many non-BP benefits, for example, maintaining lean muscle mass, especially in older adults,[17] this result would indicate that patients with stage 1 hypertension or elevated BP might safely participate in dynamic RT. The new CHEP recommendation is consistent with this interpretation of the data and this additional meta-analysis aided in the process of creating the recommendation.[37] As with the aerobic exercise recommendation, as new data become available this RT recommendation will be evaluated on a yearly basis and it might be that at some point the evidence will be strong enough to recommend RT as a potential BP-lowering strategy.

Secondary and subgroup analyses

Because of the initial small sample size and subsequently smaller subgroup sample sizes it is hard to draw specific

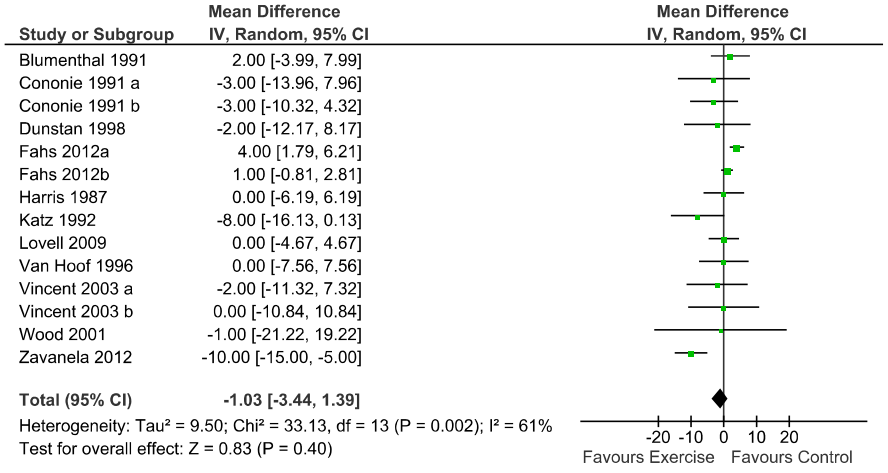

Figure 3. Pooled effect of resistance training on SBP. Average change in SBP and corresponding 95% CI for all 11 resistance training intervention groups in 9 RCTs, of note, the different training groups within an individual study are represented by an a or b. CI, confidence interval; df, degrees of freedom; IV, independent variable; RCT, randomized controlled trial; SBP, systolic blood pressure.

conclusions from the subgroups analyses (see the *Results* and *Discussion* sections of the Supplementary Material for detailed analyses and discussion), as such, no CHEP recommendations were generated from these analyses.

Other practical issues to consider

What kind of RT exercise should be used? There was insufficient information contained in the reports analyzed in the current systematic review to be able to formally assess the optimal RT program. As such, it would seem that the ACSM position statement on RT in people with hypertension would be a good model.[20] This document briefly describes BP limits, intensity of RT, appropriate technique, muscle groups, and frequency of RT, progression, sets, duration of rest periods, and mode of exercise and should be consulted for exercise specialists working with this population.

The combination of aerobic exercise and RT. Though several guidelines and position stands recommend the combination of aerobic exercise and RT,[5,20] there are little empirical data to support this. Only 1 study in the current meta-analysis combined interventions of RT and aerobic training, so that there were 3 active intervention groups—RT only, aerobic exercise only, and combined RT and aerobic exercise.[34] In this group of older participants, Wood et al.[34] found no changes in SBP or DBP after any of the training interventions. Although they did note improvements in cardiovascular fitness (measured as graded exercise test duration) and strength with the combined intervention and with RT or aerobic training alone.[34]

Acute effects of RT. The acute effects of RT on BP are complex and outside of the scope of this review. A recent review suggested that RT has a hypotensive effect on BP immediately after cessation of exercise that persists between 1 and 10 hours after RT, with the effects most prolonged after low-intensity training.[38] This might be especially true for patients with hypertension that is controlled with antihypertensive drugs.[38] However, the potential for increasing BP during RT is ever-present, as it is with aerobic exercise, and monitoring should be done when this is a consideration.[20]

Limitations

These results should be interpreted in light of some limitations. First, there are only a small number of RCTs evaluating the effect of RT on BP as a primary outcome, and this meta-analysis considers the results of relatively few participants (ie, N = 452), potentially leading to insufficient power to detect significant changes in pooled analyses. Second, the reporting quality as reflected in the risk of bias assessment is generally poor. Third, none of the studies described their analyses as intention-to-treat, which is critical for determining the efficacy and feasibility of an intervention. Fourth, the intervention protocols were generally poorly described and lacking in details. For example, reporting of adherence and compliance provide crucial insight to the success of the proposed program, yet these details were not reported. Additionally, information regarding whether the programs were delivered in individual or group formats, and who supervised the training, was often missing. The poor reporting quality is likely because many (5 of 11) of these RCTs, predate publication of the CONSORT (**Con**solidated **S**tandards **o**f **R**eporting **T**rials) guidelines.[39]

Conclusions

Results suggest that participation in RT is not harmful and does not increase BP. Despite a small statistically significant improvement in DBP, more evidence is needed before recommending RT as a specific BP-lowering therapy.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.02.010.

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Author:	Amanda M. Rossi,Gregory Moullec,Kim L. Lavoie,Gabrielle Gour-Provençal,Simon L. Bacon
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APPENDIX F

Rossi A, Moullec G, Lavoie KL, Bacon SL. Resistance Training, Blood Pressure, and Meta-Analyses. *Hypertension*. 2012;59(3):e22-3. Wolters Kluwer Health Lippincott Williams & Wilkins©

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Resistance Training, Blood Pressure, and Meta-Analyses

Amanda Rossi, Gregory Moullec, Kim L. Lavoie and Simon L. Bacon

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Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

Resistance Training, Blood Pressure, and Meta-Analyses

To the Editor:

We read with great interest the recent meta-analysis by Cornelissen et al[1] evaluating the impact of resistance training on blood pressure. This is an area that certainly needs a great deal of clarification, and the finding that dynamic and isometric resistance training results in a decrease of 3.9/3.9 mm Hg in normotensive/prehypertensive participants and a 4.1/1.5-mm Hg decrease in hypertensives provides a useful synthesis of the existent literature. However, we feel there are some methodological issues that need to be considered when interpreting these data.

First, the authors have included articles for which blood pressure was not the primary outcome of interest. Although the inclusion of such secondary data certainly helps to provide as full a picture as possible, it does have the possibility to influence the effect estimates in their meta-analyses.[2,3] For example, we have recently presented a meta-analysis of randomized, controlled trials assessing the impact of resistance exercise where blood pressure was the main outcome (included studies up to March 2010).[4] Unsurprisingly our analysis yielded fewer studies (9 articles with 11 treatment groups) compared with Cornelissen et al[1] (28 articles with 33 treatment groups). Although consistent in direction, our analysis showed a nonsignificant pooled effect of resistance training on change in systolic and diastolic blood pressure of 1.08/1.03 mm Hg. Although it is possible that the reduced sample size could account for this difference, it could also be accounted for by the bias generated by using studies where blood pressure was a secondary outcome.

Second, we were surprised that the authors did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[5] with regard to the reporting of the search strategy used and screening procedure used. Specifically, the authors provide the key words used for the search but not the search strategy, which creates potential problems for reproducibility of the data. In addition, a clear diagram depicting the number of records retrieved, retained, and eliminated at various stages (duplicates, abstract screening, full-text screening, and qualitative/quantitative analysis) is normally provide in such analyses.[5] Failing to provide this information creates the possibility of a selective reporting bias.

Although the main findings of our meta-analysis diverge from that of Cornelissen et al,[1] there is agreement between the 2 with regard to the demonstration of no detrimental effects of resistance exercise, that is, an increase in blood pressure or any intervention-related serious adverse events. Given this plus the other recognized benefits of resistance training, there seems to be no reason why individuals with high-normal blood pressure, prehypertension, or hypertension should not engage in a resistance exercise program. However, we would argue that we still need much more robust data before recommending it as a blood pressure–lowering therapy.

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Disclosures

None.

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Date: Mar 1, 2012

APPENDIX G

Rossi AM, Talbot D, Lefebvre G, Atherton J, Bacon SL. Marginal structural models for estimating the relationships between physical activity, blood pressure, and mortality.

Confirmation of submission to *HEART*.

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APPENDIX H

Rossi AM, Bacon SL, Stamatakis E, Hamer M. The association of blood pressure and physical activity on cardiovascular and all-cause mortality: the Scottish Health Survey

Confirmation of submission to *Journal of Human Hypertension*.

Detailed Status Information

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Title	THE ASSOCIATION OF BLOOD PRESSURE AND PHYSICAL ACTIVITY ON CARDIOVASCULAR AND ALL-CAUSE MORTALITY: THE SCOTTISH HEALTH SURVEY
Running Title	Physical activity, blood pressure, and mortality
Manuscript Type	Original
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Corresponding Author	Dr. Amanda Rossi (Concordia University)
Contributing Authors	Dr. Simon Bacon , Dr. Emmanuel Stamatakis , Dr. Mark Hamer
Abstract	OObjective: the purpose of this study was to specifically examine the main and interaction effects of different levels of physical activity and blood pressure on both fatal and non-fatal cardiovascular (CVD) events, and mortality. Methods: Data from the Scottish Health Survey participants recruited in 1995, 1998, and 2003 (8747 participants; age: 53.5 years, 57% women) was analyzed. Physical activity was assessed via questionnaire and classified as <1 bout/ week, 1-4 bouts/week, or 5+ bouts/week of at least 30 minute bouts of physical activity. Repeated resting blood pressure measurements were taken. Follow-up was censored to December 2007. Hospitalization and CVD history was acquired through patient-based database. Cox proportional hazards models (with interaction term) were used to calculate the risks of incident CVD and all-cause mortality. Results: There was a significant interaction between systolic blood pressure and physical activity (p= 0.014) such that doing any level of activity for the blood pressure groups < 160 mmHg reduced risk of CVD; in those with systolic blood pressure ≥ 160 mmHg, there was no change in risk. A main effect of systolic blood pressure was found for mortality (p= 0.01) No main effects for diastolic blood pressure or physical activity were noted, nor was there a significant interaction. Conclusions: The results showed that physical activity and blood pressure interact to impact CVD development, showing benefits of physical activity for individuals with systolic blood pressure < 160 mmHg. The findings suggest that physical activity may impact mortality indirectly through blood pressure.
Techniques	Not Applicable;
Subject Terms	Health sciences/Risk factors Health sciences/Diseases/Cardiovascular diseases/Hypertension
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APPENDIX I

Rossi AM, Davies E, Lavoie KL, Arsenault A, Gordon JL, Meloche B, Bacon SL. The impact of metabolic syndrome and endothelial dysfunction on exercise-induced cardiovascular changes. *Obesity*. 2013; 21(1);E143-8

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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

The Impact of Metabolic Syndrome and Endothelial Dysfunction on Exercise-Induced Cardiovascular Changes

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Objective: There is limited information regarding the synergistic or additive effects of metabolic syndrome (MS) and endothelial dysfunction (ED) on cardiovascular disease (CVD). Altered cardiovascular responses to exercise have been shown to predict future cardiovascular events as well as assess autonomic function. The present study evaluated the impact of MS and brachial artery reactivity (a proxy of ED) on peak exercise-induced cardiovascular changes.

Design and Methods: Individuals ($n = 303$) undergoing a standard nuclear medicine exercise stress test were assessed for MS. Participants underwent a Forearm Hyperaemic Reactivity test and were considered to have dysfunctional reactivity if their rate of uptake ratio (RUR) was <3.55. Resting and peak blood pressure (BP) and heart rate (HR) were measured. Reactivity was calculated as the difference between peak and resting measures.

Results: Analyses, adjusting for age, sex, resting HR, total metabolic equivalents (METs), and a history of major CVD, revealed a main effect of MS ($F = 5.51$, $\eta^2 = 0.02$, $P = 0.02$) and RUR ($F = 6.69$, $\eta^2 = 0.02$, $P = 0.01$) on HR reactivity, such that patients with MS and/or poor RUR had reduced HR reactivity. There were no interactive effects of RUR and MS. There were no effects of RUR or MS on systolic BP (SBP) or diastolic BP (DBP) reactivity or rate pressure product (RPP) reactivity.

Conclusions: The presence of decreased HR reactivity among participants with MS or poor brachial artery reactivity, combined with the lack of difference in other exercise-induced cardiovascular changes, indicates that these patients may have some degree of parasympathetic dysregulation. Further longitudinal studies are needed to understand the long-term implications of MS and endothelial abnormalities in this context.

Obesity (2013) **21**, E143-E148. doi:10.1038/oby.2012.129

Introduction

Cardiovascular disease (CVD) is responsible for approximately a third of all deaths in Canada each year, and incurs upwards of 18 billion dollars in annual health care costs (1,2). Metabolic syndrome (MS) and endothelial dysfunction (ED) are recognized as significant risk factors for CVD (3,4). However, the precise mechanisms by which MS and/or ED contribute to the development of CVD are still largely unknown. Exercise testing can be employed to evaluate cardiovascular abnormalities in patients with MS and/or ED and is often used as a diagnostic tool for latent CVD (5,6). The autonomic nervous system (ANS) is largely responsible for maintaining normal physiological functions, including regulating heart rate (HR) and blood pressure (BP) (7,8). Malfunctioning of this system has been found to have negative repercussions on cardiovascular health (9). Additionally, the ANS is crucial for readjusting and adapting these parameters when the cardiovascular system is perturbed, such as during exercise (10,11). Thus, various forms of exercise (e.g., aerobic and isometric) can be used to assess the performance of the

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The first two authors contributed equally to this work.

Disclosure: A.A. owns the patent rights for the FHR procedure (US 64,449,945 B1) and also owns 100% of SyGeSa, which owns the rights for the proprietary software used in the calculation of RUR. See the online ICMJE Conflict of Interest Forms for this article.

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ANS (12). Moreover, exercise has advantages over other methods of ANS measurement, such as microneurography, which are more involved, sometimes invasive, and costly (13).

The purpose of this study was to identify and better understand cardiovascular abnormalities in patients with MS and/or ED by examining cardiovascular changes during exercise stress testing. Previous studies have indicated a degree of ANS dysregulation in people with both ED and MS (4,14). However, to our knowledge, no studies have considered the interactive effects of these two conditions on cardiovascular responses to strenuous exercise.

Methods and Procedures

Participants

The data presented here is a subanalysis of the cross-sectional Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia (MOSMI) study. The project recruited 904 patients that were referred for exercise stress testing using single photon emission computed tomography imaging between May 2005 and December 2006. All testing was performed in the Nuclear Medicine Department at the Montreal Heart Institute. There were no exclusion criteria for age, sex, or race; however, only patients fluent in French or English were eligible. Participants were also excluded if they were pregnant or nursing, had serious non-cardiovascular related disease (e.g., cancer or chronic obstructive pulmonary disease), suffered from chronic pain (other than angina), had used non-steroidal inflammatory drugs in the past week or used an analgesic on the testing day. Ethical approval for this study was obtained through the Human Ethics Committee of the Montreal Heart Institute, and written informed consent was obtained from each participant. A subsample of the patients participating in the MOSMI study were randomly selected to undergo forearm hyperaemic reactivity (FHR) testing, and it was with this cohort of 303 men and women (for whom we had complete data sets) that this analysis was performed. The participants in this cohort were referred to the Nuclear Medicine Department at the Montreal Heart Institute for cardiovascular testing, which suggests that participants possibly already had CVD or were at risk for CVD. No significant differences for age, sex, or history of CVD were observed between the subsample and those who did not undergo FHR testing.

Procedures

All participants underwent a standard, medically required, single photon emission computed tomography exercise stress test according to standard procedures (15). This protocol consists of 2 days of testing. On day 1, the participants underwent an exercise stress test and scan. Before this test, participants were approached for the study. Following the exercise stress test, patients completed a series of questionnaires assessing psychological (e.g., Beck Depression Inventory, Anxiety Sensitivity Index, and Toronto Alexithymia Scale), socioeconomic (e.g., household composition, years of education, and family income), and medical (including information on medication usage) histories. On the second day of testing, participants completed a resting single photon emission computed tomography scan. Prior to the resting scan participants had a fasting blood sample drawn. Anthropometric measures including height, weight, and waist circumference were taken. Waist circumference was measured at the top of the iliac crest. Additionally, participants completed the FHR test.

Exercise stress testing

The stress test was performed on the treadmill following the standard modified Bruce protocol (16) in order to accommodate elderly and sedentary individuals. HR was continuously measured using a standard 12-lead ECG (Marquette Medical Systems, Milwaukee, WI). BP was measured every other minute with a manual sphygmomanometer (Welch Allyn Tycos-767 series, Skaneateles Falls, NY). All readings, for BP and HR, were taken by experienced technicians.

Brachial artery reactivity

All of the patients included in this analysis underwent FHR testing to assess brachial artery reactivity, which was used as a proxy of endothelial function in the present study. The FHR test protocol has been described previously (17). Participants were seated in front of a large field-of-view gamma camera and an occlusion cuff was inflated proximal to the right elbow to 50 mm Hg higher than their resting systolic BP (SBP) for 5 min. Once the cuff was released, 30 s were allowed to elapse before injecting the patient with technetium-99m-tetrofosmin (Myoview), through a venous catheter placed in the median antebrachial vein of the left arm at the level of the cubital fossa. Upon scanning the activity time curves of the tracer, the peak slopes of the right (hyperaemic) arm were divided by the left (control), thus calculating the rate of uptake ratio (RUR). This measure of brachial artery reactivity has been shown to predict the presence of CVD (18), has a high test-retest reliability ($r = 0.89$) (19), excellent inter- and intra-rater reliability ($r = 0.98$) (20), and is consistent with similar nuclear medicine based techniques (21). Participants were classified as having poor function if they had an RUR <3.55; this cutoff value has been previously reported to be highly correlated to CVD (17) with a lower RUR score is indicative of ED.

Metabolic syndrome

Prior to the FHR test a trained technician measured the participants' waist circumference and drew a blood sample (from the indwelling catheter inserted for the FHR test). Blood samples were analyzed by the Haematology Department at the Montreal Heart Institute, using standard protocols. Participants were categorized as having MS if they met any three of the following criteria: BP $\geq$130 mm Hg SBP or $\geq$85 mm Hg diastolic BP or antihypertensive drug treatment in patients with a history of hypertension, waist circumference $\geq$102 cm in men and $\geq$88 cm in women, fasting glucose $\geq$5.5 mmol/l (100 mg/dl) or drug treatment for elevated glucose, triglycerides $\geq$1.7 mmol/l (150 mg/dl) or drug treatment for elevated triglycerides, and HDL $<$1.03 mmol/l (40 mg/dl) for men, and $<$1.3 mmol/l (50 mg/dl) for women. All values and measurements followed American Heart Association (AHA) Guidelines for the diagnosis of MS (22).

Statistical analysis

Rate pressure product (RPP) was calculated as the product of SBP and HR/100, for any given measurement. Reactivity was measured as the difference between peak and rest measurements taken before and during testing for HR, SBP, diastolic BP (DBP), and RPP. Separate General Linear Models (GLM, using SAS's proc glm function) were performed to assess the main and interaction effects of RUR and MS on HR reactivity (ΔHR), SBP reactivity (ΔSBP), DBP reactivity (ΔDBP), and RPP reactivity (ΔRPP), adjusting for age, sex, resting cardiovascular measure (e.g., for ΔHR, resting HR was included as a covariate), total metabolic equivalents (METs) achieved during the exercise stress

TABLE 1 Participant characteristics

	All	No disease	Low RUR	MS	Low RUR +MS	*F* value[a]	*P* value[a]
N	303	103	62	67	71		
Age (years)	60 ± 10	59 ± 10	60 ± 9	61 ± 9	59 ± 10	3.45	0.064
Sex (% female)	25 (*n* = 76)	30 (*n* = 31)	29 (*n* = 18)	18 (*n* = 12)	21 (*n* = 15)	0.18	0.673
Ever smoked (% yes)	69 (*n* = 208)	60 (*n* = 62)	79 (*n* = 49)	69 (*n* = 46)	72 (*n* = 51)	1.99	0.159
Cardiovascular disease (% yes)	40 (*n* = 122)	33 (*n* = 34)	34 (*n* = 21)	45 (*n* = 30)	52 (*n* = 37)	0.32	0.570
Waist circumference (cm)	100 ± 12	94 ± 9	95 ± 11	105 ± 12	108 ± 10	0.59	0.443
BMI (kg/m^2)	27.8 ± 4.5	25.9 ± 4.0	26.4 ± 3.7	29.1 ± 4.1	30.6 ± 4.2	0.98	0.322
TG (mmol/l)	1.49 ± 0.9	1.2 ± 0.6	1.2 ± 0.6	2.0 ± 0.9	1.8 ± 1.0	1.19	0.276
Glucose (mmol/l)	5.7 ±1.3	5.3 ± 0.8	5.1 ± 0.4	6.2 ± 1.6	6.2 ± 1.6	0.24	0.624
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.4	1.5 ± 0.5	1.1 ± 0.3	1.1 ± 0.3	1.29	0.256
RUR	4.11 ± 1.7	5. 41 ± 1.44	2.64 ± 0.63	4.94 ± 1.47	2.75 ± 0.57	4.44	0.036*
Resting, baseline values							
HR (bpm)	66.9 ± 12.1	66.5 ± 11.4	67.0 ± 11.6	65.3 ± 9.9	68.7 ± 15.0	1.02	0.313
Systolic BP (mm Hg)	134.2 ± 18.4	133.5 ± 17.3	136.2 ± 18.6	134.3 ± 15.7	133.3 ± 22.1	0.77	0.382
Diastolic BP (mm Hg)	81.9 ± 10.7	81.5 ± 9.9	83.9 ± 10.4	82.3 ± 11.5	80.1 ± 11.3	3.24	0.073
RPP (mm Hg × bpm/100)	89.8 ± 21.4	88.5 ± 18.4	91.4 ± 20.7	87.9 ± 17.8	92.0 ± 28.2	0.06	0.806
Peak values							
HR (bpm)	134.1 ± 23.1	141.5 ± 21.7	134.5 ± 22.9	129.1 ± 22.6	127.6 ± 23.2	1.14	0.287
Systolic BP (mm Hg)	167.6 ± 26.0	164.8 ± 24.8	173.6 ± 26.6	168.1 ± 24.1	165.8 ± 28.4	3.36	0.068
Diastolic BP (mm Hg)	84.9 ± 11.1	85.2 ± 10.3	86.6 ± 10.0	85.3 ± 12.2	82.9 ± 11.9	2.19	0.139
RPP (mm Hg × bpm/100)	226.1 ± 56.7	233.7 ± 52.2	233.8 ± 53.6	219.9 ± 59.1	214.2 ± 61.6	0.19	0.659
Medication use (% n)							
ACE inhibitor	26	15	14	34	46	1.70	0.194
β-Blocker	29	20	14	31	54	8.34	0.004*
Statin	50	39	42	52	69	1.27	0.261
Diabetes medication	14	5	2	22	29	1.75	0.186
Total METs	8.4 ± 1.7	9.0 ± 1.8	8.2 ± 1.7	8.0 ± 1.5	7.8 ± 1.5	2.36	0.126

ACE, angiotensin-converting enzyme; BP, blood pressure; bpm, beats/minute; HDL, high high-density lipoprotein; HR, heart rate; METs, metabolic equivalents; MS, metabolic syndrome; RUR, relative-uptake-ratio; RPP, rate pressure product; BMI, body mass index; TG, triglycerides.
[a]The *F* and *P* values reflect the results from the MSxRUR interaction analysis.
*$P < 0.05$

test, and cardiac history (previous myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention) measured by self-report. These covariates were a priori defined due to their previous associations with the physiological processes under examination. As part of the review process we were requested to add smoking status as an additional covariate for which a separate series of analyses were conducted. Demographic and sample data is reported as mean ± SD. A value of $P < 0.05$ was considered statistically significant.

Results

Participant characteristics

Please refer to Table 1. The mean (SD) age of the participants was 60 (10) years and the majority were males (75%). As detailed in Table 1, 34% ($n = 103$) of the population were free of either poor RUR or MS, 23% ($n = 71$) had both poor RUR and MS, 21% ($n = 62$) had poor RUR only, and 22% ($n = 67$) had MS only. Overall, the participants had relatively average body mass index measurements (mean (SD): 27.8 ± 4.5 kg/m^2), waist circumference (mean (SD): 99.5 ± 12.1 cm), triglycerides (mean (SD): 1.5 ± 0.9 mmol/l), and HDL (mean (SD): 1.3 ± 0.4 mmol/l) levels. No between-group differences were noted. However, on average this sample had abnormally high (according to AHA guidelines (22)) fasting blood glucose levels of 5.7 ± 1.3 mmol/l indicating that a great proportion of the population studied likely had impaired glucose tolerance or insulin resistance. No differences were noted between groups for baseline, resting HR, SBP, DBP, and RPP measures (see Table 1).

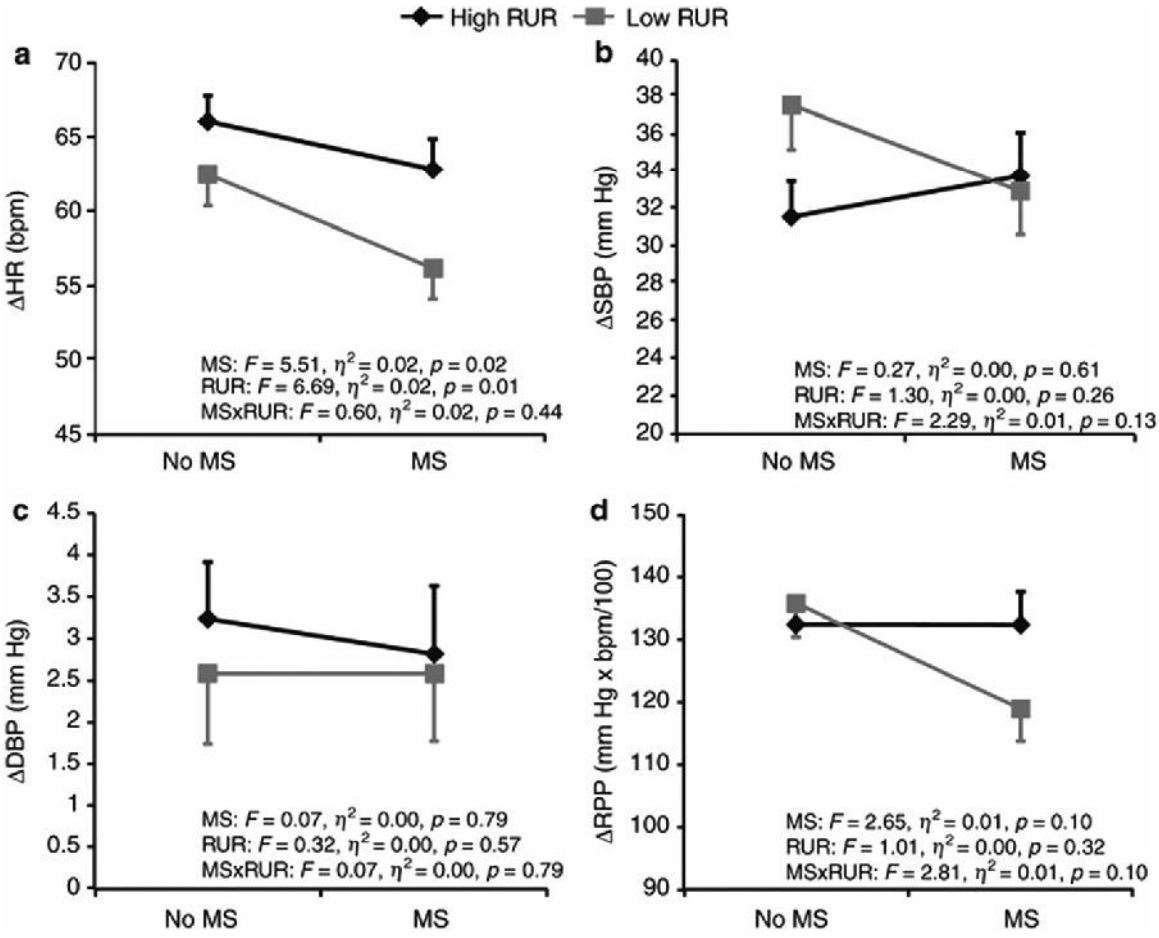

FIGURE 1 Association between metabolic syndrome (MS), relative uptake ratio (RUR), and exercise-induced cardiovascular reactivity. (**a**) Mean heart rate reactivity (ΔHR), (**b**) mean systolic blood pressure reactivity (ΔSBP), (**c**) mean diastolic blood pressure reactivity (ΔDBP), (**d**) mean rate pressure product reactivity (ΔRPP). Vertical bars represent the SE. MS, metabolic syndrome; RUR, rate of uptake ratio.

Exercise-induced cardiovascular changes

As seen in Figure 1a, there were main effects of MS ($F = 5.51$, $\eta^2 = 0.02$, $P = 0.02$) and poor RUR ($F = 6.69$, $\eta^2 = 0.02$, $P = 0.01$) on ΔHR. Patients with MS or low RUR in this study had decreased ΔHR in comparison to those without MS or ED. There was no interaction effect between low RUR and MS ($F = 0.60$, $P = 0.44$) on ΔHR. As detailed in Figure 1b and c, there were no main or interaction effects of MS or poor RUR on ΔSBP or ΔDBP. There also appears to be a trend of decreased ΔRPP among the participants with both low RUR and MS, however this result was not statistically significant (see Figure 1d). When smoking was added to these analyses there was no substantive change in the results found.

Discussion

Although no differences in baseline HR were observed between groups, the study participants with poor RUR and/or MS were found to have independent effects of decreasing ΔHR to exercise compared to those without either condition. It was also observed that MS and poor RUR did not have any multiplicative effects on the measured cardiovascular parameters during exercise. According to the collected data, the presence of poor RUR and/or MS did not influence the ΔSBP, ΔDBP, or ΔRPP. Given that both MS (23) and ED (4) have been linked to ANS dysregulation, this finding is likely reflective of autonomic dysfunction, and perhaps specific to the parasympathetic branch.

The individual components of MS have been linked to altered autonomic activity measured both systemically and regionally. A review by Tentolouris and colleagues (23) clearly outlines these associations. Acute infusion of insulin, for instance, can reduce the parasympathetic impact on cardiac function and concomitantly stimulate sympathetic nervous system (SNS) activity, as measured by HR variability, in healthy women (24). Comparison of autonomic activity in type II diabetics with and without MS displayed greater cardiac

sympathetic predominance in those with MS (25). Additionally, it has been suggested that increased SNS activity may result from insulin resistance (26). Similarly, sympathetic overactivity has been observed in obese women (23,27). Autonomic dysfunction also varies according to fat distribution, whereby those with higher visceral fat had lower baroreceptor sensitivity (28) and higher basal muscle sympathetic nerve activity compared to matched controls (29). Autonomic dysregulation has also been widely documented in those with hypertension (23,26). Overactivity of the SNS is involved in the pathogenesis of hypertension (30) and has been shown to be related to hypertension severity (31). Increased HR, greater noradrenaline spillover, baroreflex dysfunction, and elevated sympathetic activity measured by microneurography have been observed in individuals with high BP (26). Of note, baroreflex impairment and SNS overactivity are amplified when patients present with both hypertension and obesity (32). Lastly, autonomic impairment has also been associated with dyslipidemia. Acute infusion of nonesterified fatty acids and triglycerides decreased baroreceptor sensitivity in obese hypertensive individuals to a greater extent than in the healthy control group (33). These previous findings illustrate a clear relationship between autonomic dysfunction and the MS.

Similarly, ANS impairments have been observed with ED. Under normal circumstances vascular endothelial cells and the ANS operate in an antagonistic manner to maintain appropriate vessel tone; the endothelium works to produce a vasodilatory effect and the SNS is chiefly responsible for vasoconstriction. A review by Harris and Matthews (4) outlines both direct and indirect associations between ED and ANS dysregulation. Which impairment comes first in the development of CVD remains unknown; however there is evidence to suggest this relationship may be mediated by sex hormones, oxidative stress, platelet activation, the renin–angiotensin system, the hypothalamic–pituitary–adrenal axis, insulin resistance, and aging (4).

The dampened exercise HR response in participants with poor RUR and/or MS observed here may be reflective of autonomic dysregulation in these individuals because the control of HR during exercise is achieved by a fine balance between the deactivation of the parasympathetic nervous system (PNS) and concomitant stimulation of the SNS, in addition to various hormonal influences (34,35). Typically HR increases during exercise; the extent to which depends on the dose of physical activity (i.e., the intensity and duration of exercise) as well as the individual's cardiovascular fitness (36,37). The rapid augmentation of HR at the very onset of aerobic exercise results from a decrease in cardiovagal modulation of HR which continuously decreases to the point that the signal is extremely low, even undetectable, as exercise workload is increased (37). Simultaneously, there is an increase in sympathetic activation (37). Thus because PNS inhibition has been found to be largely responsible for the exercise-induced HR increases, it could be that patients with ED and/or MS have some level of dysregulation of the parasympathetic system. It is also important to acknowledge the contributing role of the SNS in regulating HR and be aware that there may also be malfunction in this division of the ANS. However, the lack of statistical support for differences in ΔSBP, ΔDBP, and ΔRPP between participants with poor RUR and/or MS and those without one or the other condition may indicate adequate functioning of the sympathetic system. It should be noted that the data presented here cannot directly confirm this statement and further investigation would be necessary to establish the relative contributions of PNS and SNS dysfunction in these populations. Whilst further research is necessary, the findings of this study suggest that there is partial dysfunction of the PNS. It still remains unknown whether it is the disease state (i.e., having ED or MS) which brings about autonomic dysregulation or vice versa.

The results of this study should be considered in light of several limitations. The participants in this study were all referred to the Nuclear Medicine Department at the Montreal Heart Institute for cardiovascular testing, meaning that they all had CVD or were likely at risk for CVD in some capacity. As the cardiovascular reactivity levels measured in this study are all relative to those without the conditions, the results may be underestimated due to the fact that they were not measured against a healthy control group. However, history of CVD was adjusted for in the statistical analysis and therefore any effect of this should be reduced. Also, the guidelines for the diagnosis of MS vary between organizations, thus if different classification guidelines, such as those of the World Health Organization, were employed within the same population, then it is likely that some participants would have been categorized differently consequently altering the results. However, because the AHA guidelines are those employed most frequently for classification of MS and the various series of diagnostic parameters differ marginally from one another, the use of the AHA guidelines is justified. Additionally, analysis of HR variability or baroreflex sensitivity could provide insight into the question of sympathetic vs. parasympathetic dysregulation. However, this analysis was not possible with the data collected and should be considered in future studies. In spite of these limitations, there are several strengths of the present study that should be noted, specifically that it sampled a large number of patients, and the testing was performed in a controlled environment. Also the measurement technique used to determine the presence of brachial artery reactivity is a reliable and validated, though not widely used, method (17). Important confounding factors such as age, sex, cardiovascular history, and total METs were adjusted for in the statistical analysis, which further strengthens the significance of the results.

Studies assessing PNS function by measuring HR variability and HR recovery have shown links with CVD outcomes/endpoints, e.g., MI, sudden cardiac death (38,39) and other comorbidities, e.g., depression (40) and thus it is plausible that PNS dysregulation is observed in pre-CVD conditions, e.g., MS and ED, and is manifested through changes in exercise HR. Though there is still debate regarding the interpretations of HR variability and HR recovery, understanding how PNS function may be altered by CVD precursors can help contribute to the prognostic value of this parameter. Future studies should consider using HR variability, HR recovery, HR spectral-analysis and/or microneurography to address questions related to the function of the ANS components, specifically PNS dysregulation in this patient population.

Given the information linking ED and MS with ANS dysregulation, it is reasonable to hypothesize that patients affected with both conditions would have worse ANS functioning. However, the data presented here does not encourage the notion of the existence of any multiplicative effects of MS and ED as would have been expected based on the frequently observed pairing of MS risk factors and various indicators of ED. Overall, the findings of this study support further research in the area of ANS function, and specifically the PNS, in regards to how malfunctioning contributes towards the origins of CVD. Additionally, it would be of significant value to explore whether or not a relationship exists between the level of ED and the

extent of ANS dysregulation. A better understanding of the aetiology of CVD, with specific attention to ANS dysregulation, would potentially lead to the formulation of new therapeutic intervention strategies, including both pharmacological aids and lifestyle regimes, intended to effectively treat CVD.

The results reported here indicate that people with MS and/or ED have some degree of ANS dysregulation. Given that only a significant decrease was observed for ΔHR it is likely that the dysregulation specifically involves PNS activity. The lack of significance for other cardiovascular parameters indicates that patients with poor RUR and/or MS may have relatively normal SNS regulation. The exact mechanisms by which ANS dysregulation occurs is still largely unknown; however, building a better understanding of the characteristics of pre-CVD conditions, such as ED and MS, research is closer to uncovering the pathogenesis of CVD, which could lead to improved treatment and early diagnosis strategies. O

Acknowledgments

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APPENDIX J

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Objectively Assessed Physical Activity, Sedentary Time, and Coronary Artery Calcification in Healthy Older Adults

Mark Hamer, Shreenidhi M. Venuraju, Avijit Lahiri, Amanda Rossi, Andrew Steptoe

Objective—Physical activity is related to lower risk of cardiovascular disease, but data relating to coronary lesions have been conflicting. These inconsistencies may in part be due to unreliable assessment of physical activity and limitations imposed by self-reported data. The purpose of this study was to determine the relationship between objectively measured physical activity and coronary artery calcium (CAC).

Methods and Results—Participants were 443 healthy men and women (mean age=66±6 years), without history or objective signs of coronary heart disease, drawn from the Whitehall II epidemiological cohort. Physical activity was objectively measured using accelerometers worn during waking hours for 7 consecutive days (average daily wear time=889±68 minutes/day). CAC was measured in each participant using electron beam computed tomography and was quantified according to the Agatston scoring system. On average, 54.4% of the sample recorded at least 30 minutes/day of moderate to vigorous physical activity (MVPA). There was no association between MVPA and presence of detectable CAC. For the participants with detectable CAC (n=283) a weak inverse relationship between MVPA (minutes/day) and log Agatston score was observed (B=−0.008, 95% CI: −0.16 to 0.00, P=0.05), although the association was no longer present after adjustments for age, sex, and conventional risk factors. No associations were seen for light activity or sedentary time.

Conclusion—Our results confirm no association between objectively assessed physical activity and CAC. Because CAC measures cannot identify more vulnerable lesions, additional studies are required to examine whether physical activity can promote plaque stability. **(*Arterioscler Thromb Vasc Biol*. 2012;32:500-505.)**

Key Words: calcification ■ coronary artery disease ■ epidemiology ■ exercise ■ prevention

Physical activity is important for maintaining cardiovascular health in older age,[1–3] although the mechanisms remain poorly understood. Evidence from training studies and epidemiological cohorts has demonstrated that various mechanisms could play a role in the cardioprotective effects of exercise, including improvement in cardiac performance, aerobic capacity, endothelial function, and inflammatory and metabolic factors.[4–10] However, the association of physical activity with coronary lesions and atherosclerotic processes remains unclear. Various studies have examined associations between physical activity and markers of subclinical atherosclerosis, although the data are equivocal.[11–19] These inconsistencies may in part be due to differences in the assessment of physical activity and limitations imposed by self-reported data. In the only study to date to have used an objective assessment of physical activity, there was an inverse association between vigorous activity and 3-year progression in common carotid artery intima media thickness.[19]

Few studies have specifically examined physical activity and coronary artery calcium (CAC), which is thought to be a more direct marker of coronary atherosclerosis than measures of carotid artery intima media thickness.[20,21] In the Multi-Ethnic Study of Atherosclerosis, self-reported brisk walking pace was associated with lower CAC in men but not in women, although null associations were observed for overall physical activity level and CAC in both sexes.[14] Because there are currently no available data on objectively measured physical activity and CAC, this formed the rationale for the present study.

Methods

Participants

A sample of participants was drawn from the Whitehall II epidemiological cohort[22] for a substudy in 2009/2010. The criteria for entry into the study included no history or objective signs of coronary heart disease, no previous diagnosis or treatment for hypertension, inflammatory diseases, or allergies. This information was confirmed by a telephone interview and verified from clinical data collected from the previous 7 phases of the main Whitehall II study. Volunteers were of white European origin, aged 56 to 79 years. Selection was stratified by grade of employment (current or most recent) to include higher

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and lower socioeconomic status participants. Participants were prohibited from using any antihistamine or anti-inflammatory medication 7 days before testing and were rescheduled if they reported colds or other infections on the day of testing. Participants gave full informed consent to participate in the study and ethical approval was obtained from the University College London Hospital committee on the Ethics of Human Research.

Physical Activity Assessment

Participants were asked to wear an accelerometer (Actigraph GT3X) mounted at the hip, which records movement on the vertical and horizontal axis, during waking hours for 7 consecutive days. The accelerometer provides a measure of the frequency, intensity, and duration of physical activity and allows classification of activity levels as sedentary, light, moderate, and vigorous. The raw accelerometry data were processed using specialist software (MAHUffe, Cambridge [http://www.mrc-epid.cam.ac.uk/Research/Programmes/Programme_5/InDepth/Programme%205_Downloads.html]) to produce a series of standardized outcome variables. All participants included in the present analysis recorded a minimum of 10 hours per day wear time for 6 to 7 days. The first and last days of data were excluded from the analysis and nonwear time was defined as intervals of at least 60 consecutive minutes of 0 count/minute (cpm). We used cutoff points previously used in an older sample of adults[23] to calculate daily times in each activity intensity band: sedentary (<1.5 metabolic equivalent [MET]): 0 to 199 cpm; light (1.5–3 MET) 200 to 1998 cpm; moderate to vigorous physical activity [MVPA] (>3 MET): ≥1999 cpm. Sensitivity analyses were also performed using a more conservative cutpoint of 0 cpm to differentiate sedentary time from activity.[24] All physical activity variables were converted to time (in minutes) per valid day.

To obtain self-reported physical activity data, we retrospectively linked our data with several previous phases (phase 5 in 1997 and phase 7 in 2004) of the main Whitehall II study. The questionnaire administered in these phases consisted of 20 items on frequency and duration of participation in walking, cycling, sports, gardening, housework, and home maintenance.[25] Frequency and duration of each activity were combined to compute hours per week of physical activity. A compendium of activity energy costs was then used to derive a MET score for each of the 20 physical activities assessed. We calculated average MVPA MET-hours/week across phases 5 and 7.

Coronary Artery Calcification

The assessment of CAC was performed using electron beam computed tomography (Imatron C-150, GE Healthcare, San Francisco, CA) as previously described.[26] In brief, 40 contiguous 3-mm slices were obtained during a single breath-hold starting at the carina and proceeding to the level of the diaphragm. Scan time was 100 milliseconds/slice, synchronized to 40% of the R-R interval. Agatston and volumetric calcium scores were calculated to quantify the extent of CAC by a single experienced investigator blinded to the physical activity and clinical data on an Aquarius workstation (TeraRecon Inc, San Mateo, CA). Because calcified volume was very highly correlated with Agatston score (Spearman $r=0.99$), we present data for Agatston score only.

Covariates

Participants reported current smoking levels. Height and weight were recorded in light clothing for the calculation of body mass index (BMI). Fasting blood samples were taken for analysis of total and high-density lipoprotein (HDL) cholesterol and triglycerides, which was measured within 72 hours in serum stored at 4°C using enzymatic colorimetric methods. Low-density-lipoprotein cholesterol was derived using the Friedewald equation. Glucose homeostasis was assessed from glycated haemoglobin (HbA1c) concentration, assayed using boronate affinity chromatography, a combination of boronate affinity and liquid chromatography. Resting blood pressure was measured 3 times (using an automated UA-779 digital monitor) with participants in a seated position, and a mean value was taken from the second and third readings.

Statistical Analysis

Based on the present physical activity guidelines,[27] we created 3 categories from the MVPA variable (<10, 10–<30, and ≥30 minutes/day). To examine differences in baseline characteristics between MVPA groups, we used χ^2 tests and 1-way analysis of variance to examine categorical and continuous variables, respectively. Test for trend was analyzed by using the /contrast subcommand in a general linear model design. In addition, we used Pearson correlation, partially adjusted for age, sex, and wear time, to examine associations between Actigraph counts/minute and risk factors. Multivariate logistic regression analyses were used to examine the association between physical activity and the presence of detectable CAC (Agatston score >0). We calculated odds ratios (OR) and 95% confidence intervals (CI) for the risk of CAC according to MVPA categories, adjusting for age, sex, Actigraph wear time, employment grade (as a marker of social position), use of statins, smoking (never/former/current smoker), resting systolic blood pressure, HDL cholesterol, triglycerides, HbA1c, and BMI. In addition, we used linear regression to examine the association between physical activity and CAC as a continuous measure, in which Agatston score was log transformed (using log [Agatston+1]). In these analyses, the data are presented both as unstandardized coefficients (B) and standardized coefficients (β) with 95% CI. The standardized coefficient reflects the association in relation to a 1–standard deviation increase in the physical activity variable. Statistical significance was denoted at $P<0.05$. All analyses were conducted using SPSS version 15.

Results

From the initial sample of 510 participants, 64 did not provide Actigraph data, and 3 had missing data on other variables. Thus, the final analytic sample comprised 443 participants (mean age=66±6 years; range, 57–79 years). Participants excluded from the analysis tended to be younger (64 versus 66 years, $P=0.007$) than those included, although there was no difference in CAC (log Agatston scores, 3.00±2.39 versus 2.60±2.47, $P=0.21$).

The sample as a whole was relatively active, and 59.8% of men and 49.3% of women recorded at least 30 minutes/day of MVPA, although men were significantly more active than women (338.0±145.0 versus 303.8±130.2 cpm, $P=0.009$). In partial correlations controlling for age, sex, and wear time, average daily counts/minute was inversely related to BMI (Pearson $r=-0.23$, $P<0.001$), triglycerides ($r=-0.15$, $P=0.001$), and HbA1c ($r=-0.10$, $P=0.04$) and positively related to HDL cholesterol ($r=0.25$, $P<0.001$). Sedentary time was related to BMI ($r=0.10$, $P=0.03$) and inversely with HDL cholesterol ($r=-0.16$, $P=0.001$), although these associations did not remain significant after adjustment for MVPA. Participants who recorded at least 30 minutes/day of MVPA were younger, were from higher work grades, and had lower BMI and lower levels of HbA1c (Table 1). There was no difference in total registered Actigraph wear time between MVPA groups.

Coronary calcium scores ranged from 0 to 3510 (median=10.8, SD=364.7), and 283 participants (63.9%) had detectable CAC. In multivariate models, the risk factors most strongly associated with odds of any detectable CAC were age (OR per year=1.09, 95% CI, 1.05–1.15), male gender (OR=3.37, 2.04–5.59), use of statins (OR=4.43, 2.23–8.67), and previous/current smoker (OR=1.70, 1.06–2.71). There was no association between physical activity counts/minute, MVPA,

Table 1. Characteristics of the Study Population in Relation to Objectively Assessed MVPA (n=443)

Variable	MVPA <10 min/d (n=51)	MVPA 10 to <30 min/d (n=151)	MVPA ≥30 min/d (n=241)	*P* Trend
Age, y	68.7±6.1	66.8±5.6	64.9±5.2	<0.001
Men, %	19 (37.3)	70 (46.4)	134 (55.6)	0.03
Highest work grade, %	14 (27.5)	53 (35.1)	102 (42.3)	0.01
Current smokers, %	5 (9.8)	8 (5.3)	11 (4.6)	0.41
Resting systolic BP, mm Hg	136.7±18.8	134.2±18.0	133.3±16.0	0.45
HDL cholesterol, mmol/L	1.69±0.41	1.67±0.48	1.76±0.50	0.17
LDL cholesterol, mmol/L	3.32±0.96	3.14±0.91	3.28±1.03	0.33
Triglycerides, mmol/L	1.43±0.77	1.44±0.75	1.33±0.65	0.25
HbA1c, %	5.85±0.85	5.75±0.67	5.64±0.30	0.02
Body mass index, kg/m^2	27.7±5.4	26.4±4.1	25.3±3.5	<0.001
Statins use, %	8 (15.7)	41 (27.2)	47 (19.5)	0.11
Log Agatston score	2.63±2.74	2.89±2.47	2.41±2.39	0.17
Total activity, min/d	175.3±80.5	229.1±59.9	271.4±66.6	<0.001
Light activity, min/d	170.4±78.6	209.9±58.7	216.8±64.5	<0.001
MVPA, min/d	4.5±3.4	19.2±5.6	54.6±21.7	<0.001
Sedentary time, min/d	700.4±143.5	654.6±67.4	623.5±72.9	<0.001
Registered wear time, min/d	875.7±100.6	883.7±55.6	894.8±60.9	0.10

Values are means±SD. MVPA indicates moderate to vigorous physical activity; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

or sedentary time and risk of detectable CAC (Table 2). After adjustment for age and sex, participants with zero detectable CAC recorded 36.0±2.0 minutes/day MVPA; those with CAC >0 and <100 recorded 38.5±1.9 minutes/day; those with CAC 100 to 400 recorded 35.4±3.0 minutes/day; and those with CAC >400 recorded 35.4±3.8 minutes/day (*P* trend=0.72). We also observed no associations between any of the physical activity variables and log-transformed Agatston score in continuous analyses (results not shown). When we performed sensitivity analysis only in participants with detectable CAC, there was an inverse association between MVPA and log transformed Agatston score (Table 3). However, the association did not persist after adjustment for age (age adjusted B in participants recording >30 minutes/day MVPA=−0.15, 95% CI, −0.60 to

Table 2. Association Between MVPA, Accelerometry Counts-Min, Sedentary Time, and Presence of Coronary Artery Calcium

	Cases/n	Age- and Sex-Adjusted, Odds Ratio (95% CI)	Model 1, Odds Ratio (95% CI)	Model 2, Odds Ratio (95% CI)
MVPA				
<10 min/d	30/51	1.00 (reference)	1.00	1.00
10 to <30 min/d	104/151	1.66 (0.82–3.38)	1.53 (0.73–3.23)	1.47 (0.69–3.12)
≥30 min/d	108/241	1.20 (0.61–2.36)	1.17 (0.57–2.39)	1.09 (0.52–2.29)
P trend		0.24	0.42	0.47
Counts per min tertile				
<252	91/149	1.00 (reference)	1.00	1.00
252–357	98/148	1.25 (0.75–2.08)	1.16 (0.67–1.99)	1.14 (0.66–1.99)
>357	95/148	1.22 (0.73–2.03)	1.17 (0.68–2.02)	1.19 (0.68–2.10)
P trend		0.65	0.81	0.82
Sedentary tertile				
<609 min/d	91/148	1.00 (reference)	1.00	1.00
609–671 min/d	98/150	1.24 (0.75–2.05)	1.25 (0.74–2.13)	1.18 (0.69–2.03)
>671 min/d	93/147	0.92 (0.56–1.52)	0.96 (0.57–1.63)	0.93 (0.54–1.59)
P trend		0.50	0.57	0.67

Model 1: adjusted for wear time, age, sex, employment grade, use of statins, smoking; Model 2: adjusted for wear time, age, sex, employment grade, use of statins, smoking, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, HbA1c, and body mass index. MVPA indicates moderate to vigorous physical activity.

Table 3. Regression of Accelerometry Data on Log Agatston Score in Participants With Detectable Coronary Artery Calcium (n=283)

	Counts/min	Sedentary, min/d	Light Activity, min/d	Moderate to Vigorous Activity, min/d
Unadjusted	(B)=−0.001 (−0.003, 0.000)*	(B)=0.001 (−0.002, 0.003)	(B)=0.001 (−0.003, 0.004)	(B)=−0.008 (−0.016, 0.000)*
	(β)=−0.099 (−0.216, 0.018)	(β)=0.039 (−0.078, 0.157)	(β)=0.019 (−0.099, 0.137)	(β)=−0.113 (−0.230, 0.004)
Model 1	(B)=0.000 (−0.002, 0.001)	(B)=0.000 (−0.002, 0.002)	(B)=0.002 (−0.002, 0.005)	(B)=−0.004 (−0.012, 0.004)
	(β)=−0.038 (−0.158, 0.082)	(β)=0.003 (−0.111, 0.118)	(β)=0.054 (−0.060, 0.168)	(β)=−0.057 (−0.176, 0.062)
Model 2	(B)=0.000 (−0.002, 0.001)	(B)=0.000 (−0.002, 0.002)	(B)=0.001 (−0.003, 0.004)	(B)=−0.003 (−0.011, 0.006)
	(β)=−0.034 (−0.153, 0.084)	(β)=−0.002 (−0.112, 0.109)	(β)=0.018 (−0.091, 0.127)	(β)=−0.037 (−0.156, 0.082)

Data are presented as unstandardized coefficients (B) with 95% CI and standardized coefficients (β) with 95% CI. Model 1: adjusted for wear time, age, and sex; Model 2: fully adjusted for wear time, age, sex, employment grade, use of statins, smoking, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, HbA1c, and body mass index.

*$P<0.05$.

0.30, $P=0.52$). The use of more conservative cut points did not change the results (results not shown).

We also ran analyses to examine the longitudinal association between self-reported physical activity (averaged from 1997 and 2004) and CAC (measured in 2009/2010), although null associations were observed (Table 4).

Discussion

The aim of this study was to use an objective assessment of physical activity to examine associations with subclinical atherosclerosis. The advantage of objectively measured physical activity is that it overcomes biases associated with self-reports, which are particularly evident when trying to recall nonstructured everyday activities.[28] Despite finding associations between physical activity and several risk factors such as BMI, lipids, and HbA1c, we found no evidence of a relationship with CAC. This is largely consistent with previous studies that have used self-reported measures of physical activity. For example, in the Multi-Ethnic Study of Atherosclerosis, no associations were observed for overall physical activity level and CAC in 6482 men and women without coronary heart disease.[14] In a sample of asymptomatic adults with at least 2 risk factors for metabolic syndrome, those who regularly engaged in physical activity (>30 minutes or 3 times/week) had a lower prevalence of advanced CAC (>75th percentile based on age and gender) compared with sedentary participants.[15] However, at least 2 other studies have also reported no association between self-reported physical activity and CAC.[16,17] In addition, a study in marathon runners and age-matched controls showed that there was no association between self-reported METs and CAC.[18] In the only study to date to have used an objective assessment of physical activity, an inverse association between vigorous activity and 3-year progression in common carotid artery intima media thickness was found.[19] In addition, this study demonstrated an association between sedentary time and subclinical atherosclerosis.

Table 4. Association Between Self-Reported MVPA (Averaged Across Phases 5 and 7 [1997/2004] of the Whitehall II Study) and Presence of Coronary Artery Calcium Assessed in 2009/10 (n=408)

MVPA Tertile	Cases/n	Age- and Sex-Adjusted, Odds Ratio (95% CI)	Fully Adjusted, Odds Ratio (95% CI)
<26 MET-h/wk	79/134	1.00 (reference)	1.00
26–39.3 MET-h/wk	90/141	1.24 (0.74–2.07)	1.17 (0.68–2.01)
>39.3 MET-h/wk	99/133	1.52 (0.87–2.64)	1.53 (0.86–2.73)
P trend		0.33	0.35

Full model contains adjustment for; age, sex, smoking, systolic blood pressure, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, fasting glucose, and body mass index. All covariates are taken from phase 5 of Whitehall II. MVPA indicates moderate to vigorous physical activity; MET, metabolic equivalent.

The largely null findings on physical activity and CAC suggest that the cardioprotective effects of exercise might act through alternative mechanisms, such as inflammatory and procoagulant processes. Indeed, recent epidemiological evidence suggests that inflammatory and hemostatic risk markers made the largest contribution to the inverse association between physical activity and cardiovascular events.[9,10] Cardiorespiratory fitness might also act as an independent risk factor, and recent data suggest that exercise capacity, chronotropic response, and abnormal heart recovery during exercise stress testing were associated with CAC burden in the Heinz Nixdorf Recall study.[29] Also, we previously demonstrated an association between walking speed (a proxy marker of fitness) and CAC in the present study sample.[26] Nevertheless, data in apolipoprotein E−/− mice have demonstrated that 6 months of exercise training promotes more stable plaque phenotype, as shown by decreased macrophage and increased smooth muscle cell content compared with untrained mice.[30] Thus, the association between physical activity and plaque stability might be more crucial than overall all atherosclerotic burden.

An emerging body of evidence has shown that excessive sedentary behavior (sitting) may be linked to increased risk for obesity,[31] dyslipidemia,[32] and impaired glucose metabolism,[33] independently of MVPA. In addition, several prospective studies have shown associations between excessive sitting and risk of incident cardiovascular disease.[34] However, these studies have been largely based on measures of self-reported television time as a proxy marker of sedentary behavior. In the present study, sedentary time was related to BMI and inversely with HDL cholesterol, although there were no associations with any other risk factors or CAC. In addition, these associations did not remain significant after controlling for MVPA. Several previous studies using

accelerometry-based measures have observed detrimental, linear associations of sedentary time with waist circumference and other metabolic risk factors,[33,35] although not all studies have confirmed these findings.[36,37] Using a different objective technique to assess sedentary behavior that involved individually calibrated minute-by-minute heart rate monitoring, Helmerhorst et al[38] demonstrated an association between time spent sedentary and higher levels of fasting insulin over 5.6 years of follow-up. The discrepancy in these findings raises the possibility that television viewing does not simply represent a broader pattern of sedentary behavior but instead is a distinct behavior that carries its own risks. It is possible that self-reported television time is able to better capture prolonged periods of sitting than the present methods of objective assessment. Indeed, the accelerometry device used in the present study could not distinguish between sitting and standing.

Limitations

Because accelerometry measures were only collected over 1 week, this may not truly reflect habitual physical activity levels. Nevertheless, other data in British adults have demonstrated strong test-retest reliability for MVPA (r=0.89 for men, r=0.76 in women), measured using accelerometers for 2 nonconsecutive weeks over a 1-month period.[39] Given that the associations found with objective physical activity data are consistent with those for self-reported physical activity averaged across 2 separate assessments, this suggests that the null associations observed are not accounted for by measurement error. The participants included in the present analysis were generally healthier than the overall Whitehall II sample and demonstrated higher activity levels compared with similar aged British cohorts.[23] Therefore, our results might not be representative of the wider community. The strengths of this study include the unique measurement of objectively assessed physical activity and CAC in a relatively large and well-characterized sample.

In summary, our results demonstrate no association between objectively assessed physical activity and CAC, which is largely consistent with existing evidence. Because CAC measures cannot reliably identify more vulnerable lesions, additional studies are required to examine whether physical activity can promote plaque stability.

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Disclosures

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