Longitudinal association between physical activity and incident risk factors of metabolic syndrome in adults

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von

Laura Cleven

KIT-Dekan: Prof. Dr. Michael Mäs

1. Gutachter: Prof. Dr. Alexander Woll
2. Gutachter: Prof. Dr. Darko Jekauc

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I am indebted and grateful to my family and friends. Thank you for your love and encouraging support over the past years.

Individuals' health remains the most important thing in life. Through personal strokes of fate, I was made aware of this circumstance. Thus, I am grateful to have the opportunity to contribute relevant information to the research topic of public health and epidemiology. This single sentence was my leading motivation throughout this thesis work.

SUMMARY

In the past decades, non-communicable diseases (NCDs) (i.e. cardiovascular disease, diabetes, chronic respiratory disease, allergy, cancer) have been significantly increasing worldwide, and are considered a major cause of morbidity and mortality. A main task of public health and epidemiology is the development of successful primary prevention strategies for NCDs, by identifying relevant determinants of health. Metabolic syndrome (MetS) is a cluster of specific risk factors for NCDs. These risk factors include central adiposity (elevated waist circumference (WC)), elevated triglycerides (TG), reduced high-density lipoprotein cholesterols (HDL) levels, elevated blood pressure (BP), and dysglycemia (elevated blood glucose (BG) levels). NCDs, especially risk factors of MetS, are caused by modifiable, behavioral (lifestyle) factors such as nutrition and physical activity (PA). PA has an impact on energy expenditure and energy balance. Thus, PA is an important factor to influence (lipoprotein) metabolism and eventually the onset of (risk of incident) MetS. Despite existing global and national recommendations on PA, research shows that most adults do not meet these PA guidelines. Furthermore, PA participation is not a stable behavior over life-time, but rather varies. Additionally, longitudinal studies with long follow-up times (> 20 years) are needed to investigate new onset or development of (risk factors of) MetS over time. Thus, the primary purpose of this thesis was to examine the longitudinal associations between different variables of PA (e.g. initial/ baseline PA, change in PA behavior over time) and incident specific NCDs (i.e. MetS) and MetS' respective risk factors.

In the first publication, a systematic review was conducted to provide an overview of the existing state of literature on the association between PA and incident NCDs (i.e. obesity, coronary heart disease, diabetes, and hypertension). A systematic search in OVID, PubMed, and Web of Science databases of literature published between 2012 and 2019 was carried out. Longitudinal studies with more than 5 years of follow-up, conducted in samples of more than 500 participants, aged ≥ 18 years, and free of the respective conditions at baseline were included. PA could be leisure-time/ habitual PA, work-related PA, transportation-related PA, organized and unorganized PA. Overall, a favorable association between PA levels and a decreased risk of incident obesity, CHD and diabetes, but not hypertension was observed. Within this review, no longitudinal study conducted in Germany was found, albeit health surveys/ longitudinal studies for adults in the context of PA and health exist in Germany. Furthermore, only few studies exist with a follow-up time longer than 20 years, but do not focus on onset of MetS, or their respective risk factors. Additionally, results of the review indicated, that only few studies

reported results for change in PA behavior over time as independent variable, whereas most of the studies focused on a one-time measurement of PA to detect the association with incident diseases. Of note, PA behavior varies over time, and NCDs and their respective risk factors also develop over a long period of time. Therefore, change in PA behavior should also be considered as predictor variable in longitudinal studies.

In the second publication, the longitudinal associations between (change in) PA variables and incident MetS among middle-aged, community-dwelling adults were examined. In this analysis, 591 individuals who were free of MetS at baseline and participated at least two times in the study were included. Habitual and sports-related PA was assessed by a self-reported questionnaire, and were considered as predictor variables. To control whether the WHO recommended levels of PA are suitable for a risk reduction of MetS, cutoff-points according to the WHO recommendation for PA were defined. Furthermore, besides PA behavior at study entry, change in PA behavior was considered as well. MetS was defined based on reduced HDL levels, elevated TG, elevated BG, elevated BP, and elevated WC as diagnosed by a physician and/ or evidenced by blood samples, and by self-reported questionnaires, and were considered as outcomes of interest. Cox proportional hazard ratios (HR) and 95 % confidence intervals (CI) using regression analyses were calculated with adjustments for age, sex, and socio-economic status. The study showed that four different sports-related PA measures were associated with a decreased risk of incident MetS, with risk reductions ranging between 29-38 %. This analysis also showed that maintaining, starting or increasing sports-related PA is associated with a lower risk of incident MetS.

In the third publication, different underlying risk factors of MetS were considered as outcomes of interest. While it is important to focus on MetS itself (please refer to the second publication), contribution of PA to the risk of new onset of respective MetS risk factors should also be examined. However, longitudinal studies reporting the association between different variables of PA and the onset of different risk factors of MetS within one analysis are scarce. Therefore, the longitudinal associations between (change in) PA with new onset of five different risk factors of MetS among middle-aged adults were examined. In this analysis, 657 adults who were free of the respective outcomes at baseline were included. Levels of habitual PA and (change in) sports-related PA were assessed by a self-reported questionnaire, and were considered as predictor variables. Incident elevated WC, elevated TG, reduced HDL, elevated BP, and elevated BG were assessed by physicians and/ or determined based on blood samples, and by self-reported questionnaires, and were considered as outcomes of interest for the analyses.

Similar to the second publication, Cox proportional HR regressions and 95 % CI with adjustment for age, sex, socio-economic status, and comorbidities at study entry related to the risk factors of MetS (i.e., elevated WC, reduced HDL, elevated TG, elevated BP, elevated BG), respectively, were calculated. This analysis showed that PA at baseline, starting PA engagement, maintaining and increasing PA level over time are associated with favorable metabolic health outcomes.

In line with the current state of research, the findings of this thesis provide further evidence of a potentially beneficial impact of sports-related PA on cardiometabolic health promotion. In particular, this thesis showed that several longitudinal studies exist, that reported associations between PA and decreased risks of incident obesity, coronary heart disease, diabetes but not hypertension (Publication I). Furthermore it was shown, that initial sports-related PA, but not necessarily habitual PA, is associated with a reduced risk of incident MetS in middle-aged adults (Publication II). Additionally, increasing or maintaining high levels of sports-related PA are associated with a reduced risk of incident MetS (Publication II). Furthermore, sports participation at study entry, particularly high levels of sports-related PA at baseline, but not habitual PA, are associated with a reduced risk of new onset of reduced HDL-cholesterols (Publication III). Starting and maintaining high levels of sports-related PA are associated with a reduced risk of onset of elevated WC, TG, BG levels, and reduced HDL, but not elevated BP (Publication III). Furthermore, this thesis showed that higher sports-related PA levels at baseline and quitting sports-related PA from baseline to follow-up were associated with an elevated risk for new onset of elevated BP (Publication III).

In addition to PA assessment based on self-report (as done in Publications II and III), future longitudinal studies should also include objective PA measurements (e.g. accelerometry) to reduce recall bias. Furthermore, dietary habits should be assessed to adjust models for potential confounders. Additionally, it remains important to have long follow-up periods to detect new onset of cardiometabolic risk factors and MetS. As a conjoint task of the global actions plan, governmental and societal structures, the prevention of risk factors of MetS is important. Similar to other epidemics, prevention and control of MetS and its risk factors should thus be a primary aim for stakeholders. Furthermore, the economic burden of physical inactivity is significant. Therefore, global action plans and national prevention strategies should consider the beneficial impact of PA (and negative impact of physical inactivity) on a population’s health. A growing body of research is demonstrating positive health benefits and a potentially protective impact of PA on NCDs and metabolic risk factors. However, on population level, numbers of incident risk factors of MetS are increasing. Despite the presence of action plans and public health strategies, which are postulating those beneficial and protective associations, individuals have problems implementing a *healthy* behavior or changing their behavior to a more healthier one. This means that there might be an intention-behavior gap, demonstrating individual's struggle with motives and barriers regarding their decision to participate in PA or not. Therefore, individual's specific needs for the implementation of a stable healthy lifestyle should be considered in intervention programs as well.

In conclusion, this thesis provides additional evidence of an association between sports-related PA and a decreased risk of new onset of MetS or MetS' individual risk factors, i.e., being physically active at baseline, as well as remaining physically active or even starting sports-related PA during follow-up, were associated with a reduced risk of incident MetS or individual risk factors of MetS. Furthermore, aside from sports participation in minutes per week, PA intensity as indicated by metabolic equivalent hours per week also appears to be an important predictor variable for incident MetS. This data shows that sports-related PA should be carried out at a rather high level and with a rather high metabolic equivalent in order to achieve favorable health outcomes, whereas habitual PA was not related to the risk of incident MetS or individual risk factors of MetS. In addition, however, the associations between PA and incident elevated BP remain weak and require further investigation. The findings of this doctoral thesis have implications for PA promotion in middle-aged adults aimed at increasing metabolic health, and underline the importance of structured PA health promotion programs and public health strategies, even at community-based levels.

ZUSAMMENFASSUNG

In den letzten Jahrzehnten haben nicht übertragbare Krankheiten (NCDs) (z. B. Herz-Kreislauf-Erkrankungen, Diabetes, chronische Atemwegserkrankungen, Allergien, Krebs) weltweit signifikant zugenommen und gelten als Hauptursache für Morbidität und Mortalität. Eine Hauptaufgabe von Public Health und der Epidemiologie besteht darin, erfolgreiche primäre Präventionsstrategien für NCDs zu entwickeln, indem relevante Determinanten der Gesundheit identifiziert werden. Das metabolische Syndrom (MetS) ist eine Gruppe spezifischer Risikofaktoren für NCDs. Diese Risikofaktoren umfassen unter anderem die zentrale Adipositas (erhöhter Taillenumfang (WC)), erhöhte Triglyceridwerte (TG), reduzierte HDL-Cholesterinwerte, erhöhten Blutdruck (BP) und Dysglykämie (erhöhte Blutglukosewerte (BG)). NCDs, insbesondere die Risikofaktoren des MetS, werden durch modifizierbare verhaltensbezogene (Lebensstil-) Faktoren wie Ernährung und körperliche Aktivität (PA) verursacht. PA beeinflusst den körperbezogenen Energieverbrauch und die Energiebilanz. Daher ist PA ein wichtiger Faktor, um den (Lipoprotein-) Stoffwechsel zu beeinflussen und somit Auswirkungen auf das Auftreten des MetS (bzw. das Risiko für dieses Ereignis) zu haben. Trotz bestehender globaler und nationaler Empfehlungen zur PA zeigen Studien, dass die meisten Erwachsenen diese Empfehlungen nicht einhalten, und dass die Teilnahme an PA kein stabiles Verhalten über die Lebenszeit hinweg ist, sondern auch variieren kann. Zusätzlich sind Längsschnittstudien mit langen Nachbeobachtungszeiten (> 20 Jahre) erforderlich, um das Auftreten oder die Entwicklung des MetS, bzw. dessen Risikofaktoren, im Laufe der Zeit zu untersuchen. Das Ziel dieser Arbeit war es daher, den längsschnittlichen Zusammenhang zwischen verschiedenen Variablen der PA (z. B. Anfangs-/Ausgangsniveau der PA, Veränderungen im körperlichen Aktivitätsverhalten im Laufe der Zeit) und dem Auftreten spezifischer NCDs (d. h. MetS) und den jeweiligen Risikofaktoren des MetS zu untersuchen.

In der ersten Publikation wurde ein systematisches Review durchgeführt, um einen Überblick über den aktuellen Stand der Literatur zum Zusammenhang zwischen PA und dem auftretend von NCDs (d.h. Adipositas, koronare Herzkrankheit, Diabetes und Hypertonie) zu geben. Dafür wurde eine systematische Literaturrecherche nach Publikationen in den Datenbanken OVID, PubMed und Web of Science durchgeführt, die zwischen 2012 und 2019 veröffentlicht wurden. Es wurden Längsschnittstudien mit einer Nachbeobachtungszeit von mehr als 5 Jahren, mit Stichprobengrößen von mehr als 500 erwachsenen Teilnehmern (Alter ≥ 18 Jahre), bei denen zu Beginn die jeweilige Erkrankung nicht vorlag, eingeschlossen. PA konnte dabei freizeitbezogene, habituelle, arbeitsbedingte, transportbezogene, organisierte und unorganisierte

Aktivitäten umfassen. Insgesamt wurde ein positiver Zusammenhang zwischen PA und einem verringerten Risiko für das Auftreten von Adipositas, KHK und Diabetes, jedoch nicht für Hypertonie festgestellt. Innerhalb dieses Reviews wurde keine in Deutschland durchgeführte Längsschnittstudie gefunden, obwohl Gesundheitssurveys/ Längsschnittstudien bei Erwachsene im Zusammenhang von PA und Gesundheitsfaktoren in Deutschland existieren. Darüber hinaus gibt es nur wenige Studien mit einer Nachbeobachtungszeit von mehr als 20 Jahren, die sich dann jedoch nicht auf das Auftreten von MetS, bzw. dessen Risikofaktoren, konzentrieren. Zusätzlich zeigen die Ergebnisse, dass nur wenige Studien Ergebnisse für die Veränderungen im PA-Verhalten im Laufe der Zeit als unabhängige Variable berichteten, während die meisten Studien sich auf eine einmalige Messung von PA konzentrierten, um den Zusammenhang mit den auftretenden Krankheiten festzustellen. Es ist zu beachten, dass das PA-Verhalten im Laufe der Zeit variiert und NCDs und ihre jeweiligen Risikofaktoren auch über einen längeren Zeitraum hinweg entstehen. Daher sollte die Veränderung des PA-Verhaltens auch als Prädiktorvariable in Längsschnittstudien berücksichtigt werden.

In der zweiten Publikation wurden längsschnittliche Zusammenhänge zwischen (Veränderungen in) PA-Variablen und dem Auftreten von MetS bei mittelalten Erwachsenen einer Gemeinde untersucht. In diese Analyse wurden 591 Personen einbezogen, die zu Studienbeginn nicht an MetS erkrankt waren und mindestens zweimal an der Studie teilgenommen haben. Die habituelle und sportliche PA wurde mittels eines selbstausgefüllten Fragebogens erfasst und als Prädiktorvariablen betrachtet. Um zu kontrollieren, ob die von der WHO empfohlenen PA-Umfänge für eine Risikoreduktion von MetS geeignet sind, wurden Schwellenwerte gemäß der WHO-Empfehlung für PA definiert. Neben dem PA-Verhalten zu Studienbeginn wurde auch die Veränderung des PA-Verhaltens berücksichtigt. MetS wurde anhand von reduzierten HDL-Werten, erhöhten TG-Werten, erhöhten BG-Werten, erhöhtem Blutdruck und erhöhtem WC diagnostiziert und/oder durch Blutproben sowie durch selbstausgefüllte Fragebögen nachgewiesen und als *outcome of interest* betrachtet. Cox-proportionale Hazardratios (HR) und 95 % Konfidenzintervalle (CI) wurden unter Berücksichtigung von Alter, Geschlecht und sozioökonomischem Status berechnet. Die Studie zeigte, dass vier verschiedene sportbezogene PA-Variablen mit einer verringerten Risiko für das Auftreten von MetS assoziiert waren, wobei die Risikoreduktionen zwischen 29-38 % lagen. Diese Analyse zeigte auch, dass die Aufrechterhaltung, der Einstieg in oder die Erhöhung sportbezogener PA mit einem geringeren Risiko für das Auftreten von MetS verbunden sind.

In der dritten Publikation wurden die verschiedenen zugrunde liegenden Risikofaktoren des metabolischen Syndroms als *outcome of interest* betrachtet. Während es wichtig ist, sich auf das MetS selbst zu konzentrieren (siehe Publikation II), sollte auch der Beitrag von PA zum Risiko eines neuen Auftretens der jeweiligen MetS-Risikofaktoren untersucht werden. Allerdings sind Längsschnittstudien, die den Zusammenhang zwischen verschiedenen PA-Variablen und dem Auftreten verschiedener Risikofaktoren des MetS in einer Analyse darstellen, rar. Daher wurden die längsschnittlichen Zusammenhänge zwischen (Veränderungen in) PA-Variablen und dem Auftreten von fünf verschiedenen Risikofaktoren des MetS bei mittelalten Erwachsenen untersucht. In dieser Analyse wurden 657 Erwachsene eingeschlossen, die zu Studienbeginn nicht am jeweiligen Risikofaktor erkrankt waren. Die Ausprägung der habituellen Aktivität und die (Veränderungen von) sportbezogene PA wurden mittels eines selbstausgefüllten Fragebogens ermittelt und als Prädiktorvariablen betrachtet. Auftretende erhöhte WC, erhöhte TG, reduziertes HDL, erhöhter BP und erhöhte BG wurden von Ärzten und/oder auf Basis von Blutproben sowie mittels selbstausgefüllter Fragebögen erfasst und als *outcome of interest* für die Analysen betrachtet. Ähnlich wie in der zweiten Publikation wurden Cox-proportionale HR-Regressionen und 95%-CI mit Korrekturen von Alter, Geschlecht, sozioökonomischen Status und Begleiterkrankungen bei Studieneintritt im Zusammenhang mit den Risikofaktoren des MetS (d.h. erhöhte WC, reduziertes HDL, erhöhte TG, erhöhter BP, erhöhter BG) berechnet. Diese Analyse zeigte, dass die PA zu Studienbeginn, ein Einstieg in die PA, die Aufrechterhaltung und die Erhöhung des PA-Levels im Laufe der Zeit mit positiven Ergebnissen für die metabolische Gesundheit verbunden sind.

Entsprechend dem aktuellen Stand der Forschung liefern die Ergebnisse dieser Dissertation weitere Belege für eine potenziell positive Auswirkung von sportbezogener PA auf die Verbesserung der kardiometabolischen Gesundheit. Diese Arbeit zeigt insbesondere, dass mehrere längsschnittliche Studien existieren, die Zusammenhänge zwischen PA und einem verringerten Risiko für Adipositas, koronare Herzkrankheit und Diabetes, jedoch nicht für Hypertonie berichteten (Publikation I). Darüber hinaus wird gezeigt, dass initiale sportbezogene PA, nicht aber notwendigerweise habituelle Aktivität, mit einem reduzierten Risiko für die Entstehung des metabolischen Syndroms bei mittelalten Erwachsenen verbunden ist (Publikation II). Eine Erhöhung oder eine stabile Aufrechterhaltung hoher sportbezogener Aktivitätsumfänge ist mit einem reduzierten Risiko für das Auftreten des metabolischen Syndroms verbunden (Publikation II). Eine hohe Ausprägung sportbezogener körperlicher Aktivität zu Studienbeginn, jedoch nicht die habituelle Aktivität, sind mit einem reduzierten Risiko für das Auftreten von reduziertem HDL-Cholesterinwerten bei mittelalten Erwachsenen verbunden (Publikation III).

Zusätzlich wird gezeigt, dass ein Einstieg in sportbezogene PA und eine stabile Ausprägung sportbezogener PA mit einem reduzierten Risiko für das Auftreten von erhöhtem Taillenumfang, TG, BG-Werten und reduziertem HDL-Cholesterinwerten verbunden ist, jedoch nicht für erhöhten Blutdruck (Publikation III). Hohe sportbezogene PA zu Studienbeginn und die Beendigung der sportbezogenen PA vom Studienbeginn bis zum Ende des Beobachtungszeitraums sind mit einem erhöhten Risiko für das Auftreten von erhöhtem Blutdruck verbunden (Publikation III).

Zusätzlich zur Beurteilung der PA anhand von Selbstauskünften wie es in den Publikationen II und III durchgeführt wurde, sollten zukünftige Längsschnittstudien auch objektive PA-Messungen (z.B. mittels Beschleunigungsmessung) zur Reduktion von Verzerreffekten einbeziehen. Des Weiteren sollten in diesen Studien auch die Ernährungsgewohnheiten der Probanden erfasst werden, um die gerechneten Modelle für potenzielle Verzerrungen in Bezug auf Ernährung anpassen zu können. Es bleibt nach wie vor wichtig, in diesen Studien lange Beobachtungszeiträume zu haben, um das Auftreten neuer Risikofaktoren und MetS-Fälle erkennen zu können. Es ist die gemeinschaftliche Aufgabe von globalen Aktionsplänen, staatlicher und gesellschaftlicher Strukturen das Risiko für das Auftreten von MetS zu verringern. Wie bei anderen Epidemien sollte die Vermeidung und Kontrolle von MetS und dessen Risikofaktoren daher ein vorrangiges Ziel für die Beteiligten sein. Darüber hinaus ist die wirtschaftliche Belastung durch körperliche Inaktivität erheblich. Daher sollten globale Aktionspläne und nationale Präventionsstrategien den positiven Einfluss von PA (und den negativen Einfluss von körperlicher Inaktivität) auf die Gesundheit der Bevölkerung berücksichtigen. Eine wachsende Anzahl von Studien zeigt positive gesundheitliche Auswirkungen und einen potenziell schützenden Einfluss von PA auf NCDs und metabolische Risikofaktoren. Trotz der Vorhandensein von Aktionsplänen und öffentlichen Gesundheitsstrategien, die diese positiven und schützenden Zusammenhänge postulieren, haben Einzelpersonen Probleme damit ein gesundes Verhalten zu implementieren oder ihr Verhalten in ein gesünderes zu ändern. Dies bedeutet, dass es möglicherweise eine Diskrepanz zwischen ihrer Absicht und ihrem Verhalten gibt, die die Schwierigkeiten von Einzelpersonen bei der Entscheidung zur Teilnahme an PA oder deren Verhinderung zeigt. Daher sollten in Interventionsprogrammen auch die spezifischen Bedürfnisse von Einzelpersonen für die Umsetzung eines stabilen und gesunden Lebensstils berücksichtigt werden.

Zusammenfassend liefert diese Arbeit zusätzliche Belege für einen Zusammenhang zwischen sportbezogener PA und einem verringerten Risiko für das Auftreten des MetS oder einzelner Risikofaktoren des MetS. Sowohl PA zum Studieneintritt als auch eine Aufrechterhaltung oder sogar eine Erhöhung sportbezogener PA während des Nachbeobachtungszeitraums wurden mit einem reduzierten Risiko für das erstmalige Auftreten des MetS oder einzelner Risikofaktoren des MetS in Verbindung gebracht. Abgesehen von der wöchentlichen Dauer der sportlichen Betätigung in Minuten pro Woche scheint auch die Intensität der PA, wie sie in metabolischen Äquivalentstunden pro Woche angegeben wird, eine wichtige prädiktive Variable für das erstmalige Auftreten des MetS zu sein. Diese Daten zeigen, dass sportbezogene PA eher in einem hohen Umfang und eher mit einem hohen metabolischen Äquivalent durchgeführt werden sollte, um positive Gesundheitsergebnisse zu erzielen, während habituelle Aktivitäten nicht mit dem Risiko für das erstmalige Auftreten des MetS oder einzelner Risikofaktoren des MetS in Verbindung standen. Die Zusammenhänge zwischen PA und dem erstmaligen Auftreten eines erhöhten Blutdrucks bleiben jedoch schwach und erfordern weitere Untersuchungen. Die Ergebnisse dieser Doktorarbeit haben Implikationen für die Förderung von PA bei Erwachsenen mittleren Alters zur Verbesserung der metabolischen Gesundheit und unterstreichen die Relevanz strukturierter Programme zur Förderung der körperlichen Gesundheit und öffentlicher Gesundheitsstrategien, auch auf Gemeindeebene.

CONTENT

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PREFACE

Parts of this work have been published or have been submitted for publication. Thus, the following chapters can be read independently from each other:

Chapter 2: Cleven, L., Krell-Roesch, J., Nigg, C. R., & Woll, A. (2020). The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. *BMC public health, 20*(1). 726. https://doi.org/10.1186/s12889-020-08715-4

Chapter 3: Cleven, L., Krell-Roesch, J., Schmidt, S. C. E., Dziuba, A., Bös, K., Jekauc, D. & Woll, A. (2022). Longitudinal association between physical activity and the risk of incident metabolic syndrome in middle-aged adults in Germany. *Scientific reports, 12*(1). https://doi.org/10.1038/s41598-022-24052-5

Chapter 4: Cleven, L., Dziuba, A., Krell-Roesch, J., Schmidt, S.C.E., Bös, K., Jekauc, D. & Woll, A. (2023, under review). Longitudinal associations between physical activity and five risk factors of metabolic syndrome in middle-aged adults in Germany. *Frontiers in Public Health.*

1 GENERAL INTRODUCTION

1.1 EPIDEMIOLOGY AND PUBLIC HEALTH – DEFINITIONS AND BASIC CONCEPTS

This thesis addresses research questions in the areas of sport science, public health and epidemiology. Originated in evidence-based medicine, epidemiology and knowledge derived from epidemiologic research is important to inform evidence-based public health strategies (Jenicek, 1997; Kurth, 2006).

By combining the research interests of the respective scientific fields (e.g. medicine, sport science, health sciences/ public health), specific criteria and methods of epidemiology are applied. By understanding the underlying conditions as well as risk and protective factors of diseases as derived from the reports of epidemiological studies, health-politicians are empowered to make specific recommendations, and implement or improve intervention or prevention approaches (please refer to Figure 1). With regard to public health strategies, primary prevention of diseases, is one major task and has a potentially beneficial impact on the population as a whole, or certain populations or groups of persons at risk (Kurth, 2006).

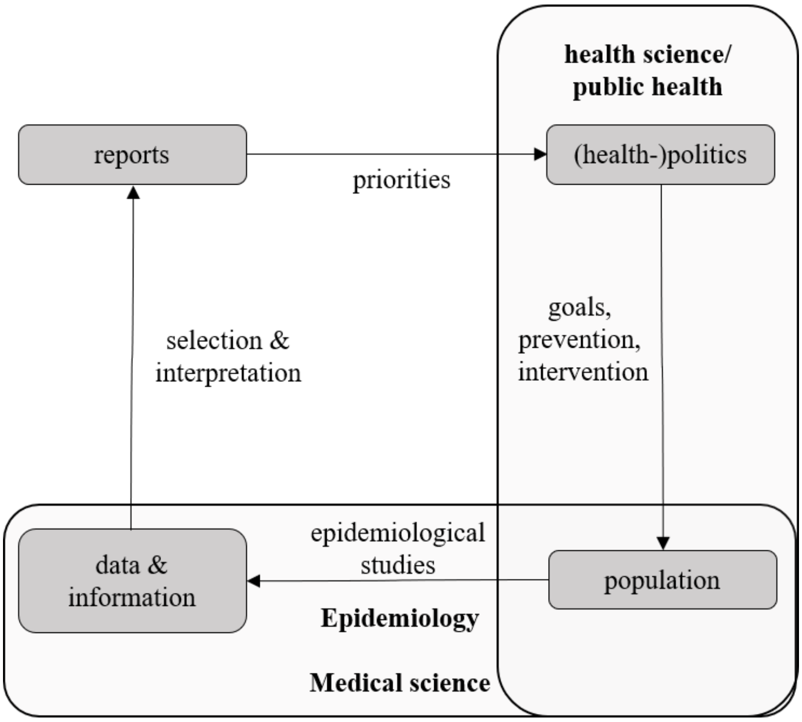


FIGURE 1: ASSOCIATION BETWEEN EPIDEMIOLOGY AND HEALTH POLITICS (BASED ON KURTH, 2006)

Health science and public health, respectively, describe an interdisciplinary research field in which the development of health and disease in the population, determinants of health, and the equity of need and efficiency of the structures of the health care system are systematically examined (Hurrelmann et al., 2015). Furthermore, according to the World Health Organization (WHO), public health includes all actions aimed at preventing diseases (i.e., primary prevention and disease prevention), promoting health, prolonging lives of all population groups, and creating healthy living conditions (Acheson, 1988). In German literature, public health and health science are often considered to be the same research field. However, public health is originally more related to the politically structured public health, whereas health science has a more pronounced interdisciplinarity character (e.g. including different research fields such as social science, political science, environmental science, psychology, medicine, and sports science) (Hurrelmann et al., 2015; Nowak et al., 2022). To this end, public health uses both qualitative and quantitative methods derived from social science as well as from epidemiology (Nowak et al., 2022). Epidemiology, in contrast, can be described, as a "the study of the distribution and determinants of health and illness in populations" (Ward et al., 2012).

Both, public health and epidemiology have a main focus on determinants of health. Thus, for a successful primary prevention, it is necessary to identify determinants of health. There are different models for systematization of those determinants. Commonly, they describe the influence of the environment on health on different layers. In addition to the focus on individual risk factors, they include the impact of the physical and social environment as well as the impact of the society (e.g. Barton & Grant, 2006; Dahlgren & Whitehead, 1991; WHO Commission on Social Determinants of Health, 2008). Such models are needed and helpful, for a structured development of health intervention on the population level (Nowak et al., 2022).

Each scientific field has its specific theories, models, methods and criteria (Neumeyer-Gromen et al., 2006). From an epistemological point of view, epidemiology asks for the causality of etiology either in individuals or on population level (Neumeyer-Gromen et al., 2006). Theoretical questions such as 'Why do diseases occur?', questions for models such as 'How do biological, social or psychological processes work?', and questions for criteria such as 'What can be used to test the etiological significance of individual epidemiological studies?' are asked (Neumeyer-Gromen et al., 2006). Epidemiology focuses on the distribution of diseases and therefore uses specific criteria (Younger & Chen, 2016). To determine the underlying mechanism, specific statistical methods (e.g. simple/ multiple linear regression, multiple logistic regression, Cox proportional hazard ratio (HR) regression) are used (Cox, 1972; Younger & Chen, 2016).

For this purpose, epidemiological estimations are needed for a precise estimation of the frequency and distribution of a certain (medical) condition (referred to as prevalence), or of the effect of an exposure (e.g., lifestyle factors such as physical activity (PA)) on the onset of a disease (referred to as incidence). Thus, prevalence focuses on the existing states and measures the frequency of existing diseases (Younger & Chen, 2016). Incidence focuses on new onset of events or changes, and measures the occurrence of new cases of diseases in a specific population over a specific time period (Younger & Chen, 2016). Different types of study designs such as cohort, case control, cross-sectional and ecological studies are suitable to detect those determinants (Younger & Chen, 2016). In epidemiological statistics, there are different options to report a relation of interests or to quantify effects and associations between determinants and diseases. Risk ratio (RR), odds ratio (OR), and HR, are commonly used (George et al., 2020). A RR is the ratio of two risks, and also expressed as relative risk. It expresses how much more risk an individual in one category bears compared to an individual in another category (George et al., 2020).

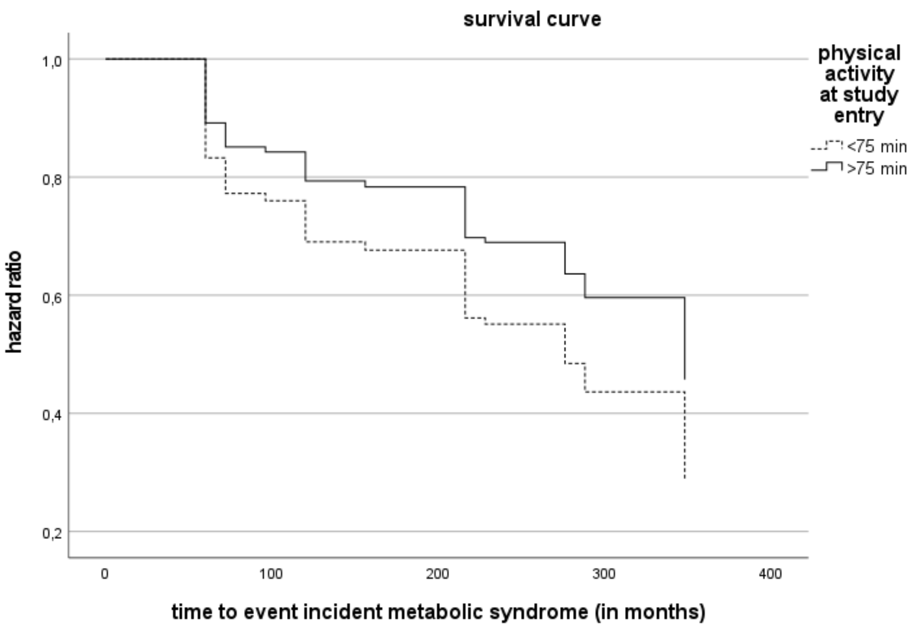


FIGURE 2: EXAMPLE OF AN SURVIVAL CURVE

However, RR cannot be used in any analysis, because the risk in a sample is an estimation of a risk in a population. Thus, the sample must be representative for the population (George et al., 2020). OR reports the number of events of interest (e.g. events of MetS) in relation to the number of events not of interest (George et al., 2020). A HR is a comparison of two hazards and is often reported in longitudinal studies. Through comparison of the slopes of the curves, it indicates how quickly two survivorship curves are diverging (George et al., 2020). For an example, please refer to Figure 2. However, OR and RR do not take into account time change in those relations, and only consider relations at one timepoint (static), whereas HRs also consider rate changes in time (dynamic) and thereby calculate a specific relation (George et al., 2020).

In addition, confidence intervals (CI) and p-values are considered. A 95 % CI indicates, that on average 95 % of the sample would meet the true population statistic within their respective 95 % CI. A p-value indicates the probability that the sample statistic was produced from a random sampling of population (George et al., 2020).

1.2 METABOLIC SYNDROME – OUTCOME OF INTEREST OF THIS THESIS

Furthermore, this thesis addresses research questions from a medical and from a health scientific point of view.

From a medical point of view, specific diseases such as infectious or non-communicable diseases (NCDs) can be addressed in research studies. In the past decades, the frequency of NCDs (e.g. cardiovascular disease, diabetes, chronic respiratory disease, allergy, cancer) has been significantly increasing in both developed and developing countries worldwide, and NCDs are considered a major cause for morbidity and mortality (Boutayeb, 2006; Hanson & Gluckman, 2011; Isomaa et al., 2001; Saklayen, 2018; Wagner & Brath, 2012). NCDs are the leading global cause of death, and account for 74 % of deaths worldwide (Bigna & Noubiap, 2019; World Health Organization, 2022b). Causes of NCDs include but are not limited to non-modifiable (e.g. age, gender, family history, genetics, personality, race) and modifiable risk factors (e.g. smoking, overweight, stress, alcohol, dietary patterns, physical inactivity) (Boutayeb, 2006; Saklayen, 2018; World Health Organization, 2022b); with modifiable behavioral risk factors being the most common causes of NCDs.

Metabolic syndrome (MetS) is a cluster of specific risk factors for NCDs. These risk factors include central adiposity (elevated waist circumference (WC)), elevated triglycerides (TG), reduced high-density lipoprotein cholesterols levels (HDL), elevated blood pressure (BP), and dysglycemia (elevated glucose levels (BG)). In medical literature, MetS is also referred to as syndrome X, cardiometabolic syndrome, insulin resistance syndrome, Reaven’s syndrome, CHAOS (as an abbreviation for coronary artery disease, hypertension, atherosclerosis, obesity, and stroke), and the Deadly Quartet (Haffner et al., 1992; Kaplan, 1989; Schindler, 2007; Sirdah et al., 2011). Specific cut off points for the five risk factors of MetS have been defined in the medical literature and are commonly used in research (Table 1). A person presenting with three out of five risk factors may be diagnosed as having MetS (Alberti et al., 2009).

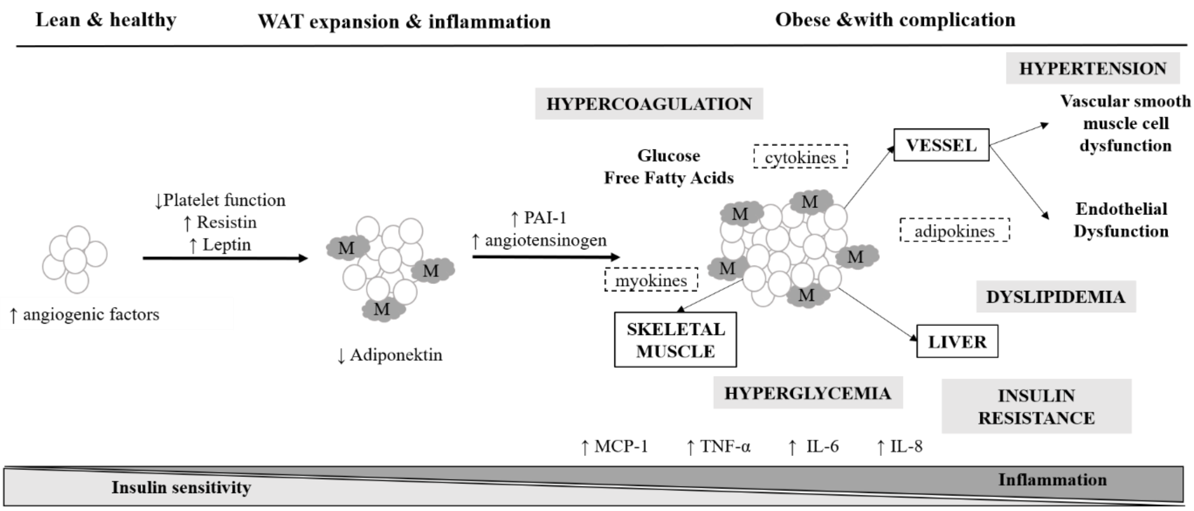
TABLE 1: CUT OFF CRITERIA OF METABOLIC SYNDROME (BASED ON ALBERTI ET AL., 2009)

Measure	Categorial cut off point	
Elevated waist circumference	male female	≥ 102 cm ≥ 88 cm
Elevated triglycerides		≥ 150 mg/dL drug treatment
Reduced HDL-cholesterols	male female	< 40 mg/dL < 50 mg/dL
Elevated blood pressure	systolic diastolic	≥ 130 mmHg ≥ 85 mmHg drug treatment
Elevated fasting glucose		≥ 100 mg/dL drug treatment

Abbreviation: cm= centimeters; mg= milligrams; dL= deciliter; mmHg= millimeters of mercury; HDL= high-density lipoprotein

It is estimated that the prevalence of MetS ranges between 20-25 % worldwide in the adult population, and reaches about 80 % in diabetes patients (Belete et al., 2021; do Vale Moreira et al., 2020). The global incidence may be estimated based on the incidence of diabetes as it often parallels the incidence of MetS. Thus, overall, it has been estimated that MetS affects about one quarter of the world population (Saklayen, 2018). These numbers are alarming, particularly considering the economic impact of MetS on health care systems (Saklayen, 2018; Scholze et al., 2010).

Research has shown that several (lipoprotein) metabolic processes underly the development of MetS (Saklayen, 2018). Signaling molecules (i.e. hormones, growth factors, proteins, bioactive substances, immune cells), such as cytokines, adipokines, coagulation molecules, hypertension molecule, and adipocyte-related molecules play a role in the development of MetS (Dominguez & Barbagallo, 2016; Vykoukal & Davies, 2011) as they lead to progression from lean and healthy to white adipose tissue (WAT) expansion, and inflammation by an increase in adipocyte mass (Figure 3). WAT stores energy in form of TG. The expansion of WAT is associated with an angiogenic response and an increase in the infiltration of macrophages into WAT. Furthermore, an excess of energy intake results in a shift of energy storage from adipose tissue to the liver and skeletal muscle (Dominguez & Barbagallo, 2016; Vykoukal & Davies, 2011). The visceral WAT alter their production of adipokines and cytokines, leading to increased inflammation, loss of insulin sensitivity (development of insulin resistance) and to hypertension, hyperglycemia, dyslipidemia, and a hypercoagulable status (Vykoukal & Davies, 2011).



Abbreviations: White circles= white adipose tissue (WAT); M= macrophage; PAI-1= plasminogen activator inhibitor-1; MCP-1= monocyte chemoattractant protein-1; TNF-α= tumor necrosis factor; IL-6= Interleukin-6; IL-8= Interleukin-8

FIGURE 3: METABOLIC DEVELOPMENT OF METABOLIC SYNDROME (BASED ON VYKOUKAL & DAVIES, 2011)

These morbidities lead to dysfunction in skeletal muscle, liver and microcirculations (Vykoukal & Davies, 2011). A chronic inflammation is associated with visceral obesity induced insulin resistance in the liver and characterized by adipokines and cytokines such as tumor necrosis factor-α, free fatty acids, interleukin-1, interleukin -6, leptin, resistin by inhibiting insulin signaling, which in turn causes impaired suppression of glucose production, which is then leading to hyperglycemia (Vykoukal & Davies, 2011). Vascular smooth muscle cell contraction and growth is modulated by multiple interacting humoral and mechanical factors (Touyz, 2000; Vykoukal & Davies, 2011). Changes in vascular structure and function (i.e. wall thickening, abnormal tone), increases peripheral resistance and appear to be the fundamental hemodynamic abnormality in hypertension (Vykoukal & Davies, 2011). As a proinflammatory state of MetS, endothelial dysfunction are induced by adipose tissue-resident macrophages and adipocytes in the adipose tissue and by the consequences of hyperglycemia, elevated lipoproteins, and hyperinsulinemia in the vasculature and within organ microcirculations (Potenza et al., 2009; Vykoukal & Davies, 2011). As underlying risk factors of diseases, MetS increases the risks of diseases like cardiovascular disease, heart failure, stroke, type 2 diabetes mellitus, and cardiovascular mortality (Belete et al., 2021; Cankurtaran et al., 2006; Scholze et al., 2010). Both prevalence and incidence of MetS increases with age, as there are many commonalities in biochemical changes of aging process and MetS (Saklayen, 2018; Stout et al., 2017).

1.3 PHYSICAL ACTIVITY – EXPOSURE OF INTEREST OF THIS THESIS

From a health scientific point of view, lifestyle behavior plays an important role when it comes to energy expenditure and energy balance (Saklayen, 2018). Thus, besides nutrition, PA can be considered as important contributor to cardiometabolic health, and potentially prevents the onset of risk factors of MetS. As stated by the WHO, PA is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" (World Health Organization, 2022c).

On a physiological level, PA has an impact on cardiovascular (i.e. improvement in oxygen uptake capacity and oxygen transport capacity; reduction of heart rate; increase in stroke volume), hemodynamic (i.e. improvement in blood flow; increase in blood clotting readiness), metabolic (i.e. increase in mitochondria volume; improvement of enzyme activity of the musculature; change of cholesterol composition by improvement of high-density to low-density ratio), and endocrinological systems (i.e. increase in catecholamines, cortisol, growth hormones), amongst others (Boström et al., 2012; Malm et al., 2019; Woll & Bös, 2004). Furthermore, on an endocrinological level, an increase in the exercise-induced hormone Irisin by the skeletal muscle, can cause an increase in energy expenditure by transforming white fat cells into brown fat cells (brown-in-white or brite cells). This leads to an improvement in glucose homeostasis (Boström et al., 2012; Kokkinos, 2012).

Due to the direct impact on bodily functions, PA has a positive impact on an individual's health. Based on results from randomized-controlled trials and observational studies, higher levels of PA may have a protective effect on various health conditions including but not limited to overweight and obesity (Madjd et al., 2016), coronary heart disease (CHD) (Colditz et al., 2016; Hambrecht et al., 2000), type 2 Diabetes mellitus (Church et al., 2010; Johannsen et al., 2013), hypertension (Nelson et al., 1986; Stewart et al., 2005), and hyperglycemia (Avery & Walker, 2001; Fritz & Rosenqvist, 2001). Additionally, longitudinal studies have become available that examined the association between PA and new onset of NCDs (Kannel et al., 1986; Leon, 1987; Paffenbarger et al., 1970; Sesso et al., 2000; Sherman et al., 1994). In addition, there is an association between higher PA and lower all-cause mortality and cardiovascular disease mortality (Blond et al., 2020; Ekelund et al., 2019; Rütten & Pfeifer, 2017; World Health Organization, 2020).

National and international guidelines exist to promote PA in the general population (Rütten & Pfeifer, 2017; World Health Organization, 2020). For adults, it is recommended to undertake regular PA. They should engage in at least 150-300 minutes of moderate-intensity aerobic PA, or at least 75-150 minutes of vigorous-intensity aerobic PA, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, in order to achieve health benefits. For additional health benefits, they should carry out muscle-strengthening activities at moderate or higher intensity that involve all major muscle groups on two or more days a week (World Health Organization, 2020). Older adults (> 65 years) should engage in multicomponent PA that emphasizes functional balance and strength training at moderate or higher intensity, on three or more days a week, to enhance functional capacity and prevent falls (World Health Organization, 2020). For adults, who are not meeting the guideline recommendation, even engaging in some PA is better than not engaging in any PA at all (Rütten & Pfeifer, 2017; World Health Organization, 2020).

Unfortunately, research shows that most adults do not meet these PA guidelines. Worldwide, 27.5 % of the world's adult population do not meet the recommended level of PA with differences in age, sexes, regions, countries. Furthermore, PA decreases with age, despite being a well-known protective factor for various health-related outcomes (World Health Organization, 2022a). On the other hand, being physically inactive is a major contributor or cause for the uprising numbers of NCDs.

Besides its direct impact on the body, a certain lifestyle (i.e. nutrition, PA) may influence the body's health to a later point in time (Saklayen, 2018). In order to elicit potential health benefits, general PA engagement on the one hand, and stability of sports participation on the other hand appear to be important factors (i.e. Friedman et al., 2008; Mertens et al., 2017). However, in adults, reported levels of sports engagement over life-time vary, with correlation coefficients from 0.11 to 0.61 and are rather unstable (i.e. Armstrong & Morgan, 1998; Mertens et al., 2017; Mulder et al., 1998). Therefore, change in PA behavior over time plays an important role, and should be considered as predictor variable in research on onset of NCDs and their respective risk factors as outcomes of interest. Furthermore, as NCDs are developing over a long period of time, longitudinal studies are needed to investigate longitudinal associations between modifiable risk factors and risk of new onset of these diseases.

Summary

This thesis focuses on PA (predictor variables) and the risk of new onset of MetS (outcome variables) in adults. To date, it is well-established that …

- …MetS is a cumulation of specific risk factors of NCDs.
- …prevalence and incidence of MetS increases with age, as the underlying biochemical processes change with age.
- …NCDs, especially risk factors of MetS, are caused by modifiable behavioral factors like nutrition and PA, amongst others.
- …PA has an impact on energy expenditure and energy balance. Thus, PA is an important factor to influence (lipoprotein) metabolism and eventually the onset of (risk of incident) MetS.
- …PA is not a stable behavior but rather varies across life-time.
- …Longitudinal studies with long follow-up periods (> 20 years) are needed to investigate the development of onset of (risk factors of) MetS.

1.4 AIM OF THIS THESIS

The aim of this thesis was to examine the longitudinal associations between different types of PA (predictor variables) and incident specific NCDs (i.e., MetS; outcome variables) and their respective risk factors. Thus, it focusses on the possibilities for primary prevention of NCDs.

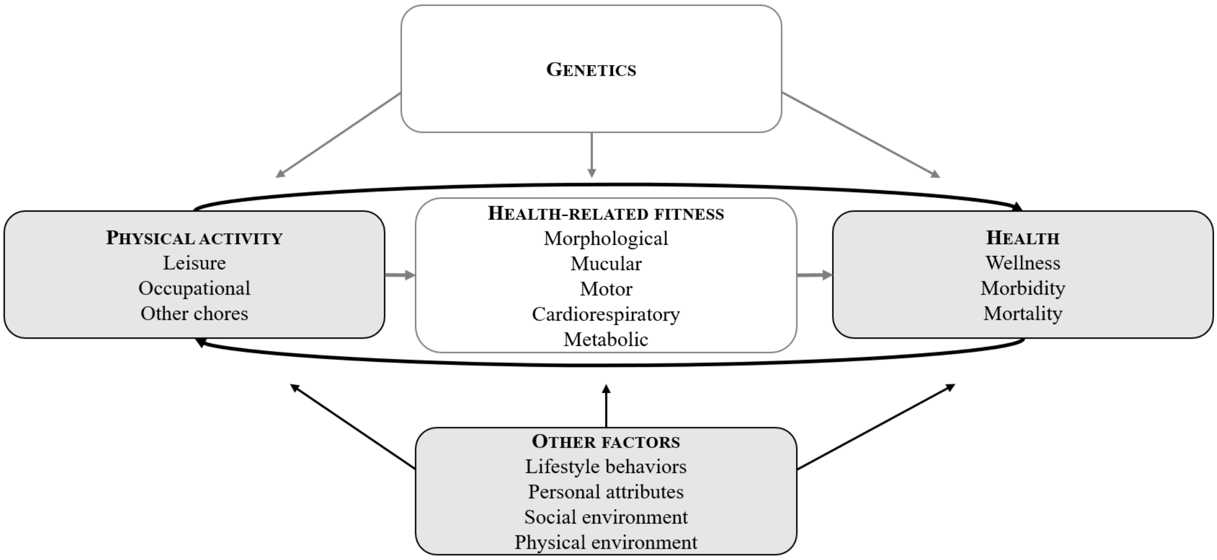


FIGURE 4: MODEL OF THE ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, HEALTH-RELATED FITNESS, AND HEALTH STATUS (BASED ON BOUCHARD ET AL., 2012)

The thesis builds on the model of the association between PA, health-related fitness and health status by Bouchard et al. (2012) (please refer to Figure 4). This model is one of the most prominent models in health sciences to explain the various complex associations and reciprocal dependencies between PA, fitness and health. In addition, other factors such as genetics, social environment or lifestyle factors have an impact as well. Therefore, the associations between PA, health-related fitness and health may not be interpreted in a causal way. For example, PA is associated with increases in cardiorespiratory fitness, which then leads to an improvement of health. However, this favorable outcome may occur regardless of an increase in fitness (Bouchard et al., 2012).

In this thesis, I will focus on the associations highlighted in grey (please refer to Figure 4), assuming that PA will improve the (lipoprotein) metabolism and will yield in an improvement of health status (i.e. decreased risk of new onset of MetS and it's respective risk factors).

1.5 RESEARCH QUESTIONS ADDRESSED BY THIS THESIS

Three research questions were addressed in this thesis. Please refer to Figure 5 for a visual display of the structure of this thesis. In a first step, a systematic review was conducted to provide an overview of the existing body of literature, addressing the following research question:

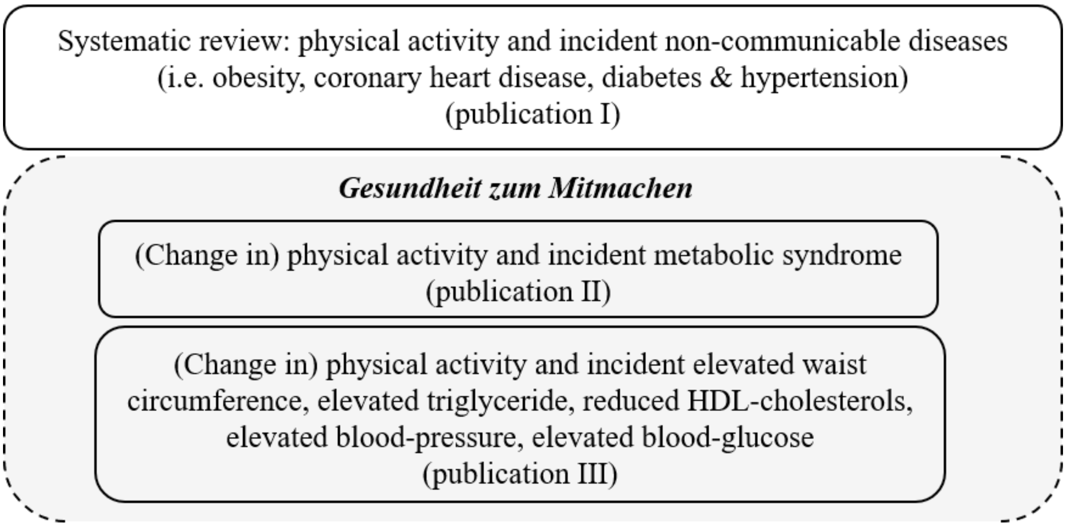


FIGURE 5: STRUCTURE OF THE THESIS

Question 1: Is there an association between physical activity and incident non-communicable diseases (i.e. obesity, coronary heart disease, diabetes & hypertension)?

This review was based on a previous review published in 2012 that reported an association between PA and type 2 diabetes mellitus, coronary heart disease (CHD), overweight/ obesity and dementia (Reiner et al., 2013). Therefore, a systematic review on the longitudinal association between PA and incident obesity, CHD, diabetes and hypertension was conducted by including literature published between 2012 and 2019 (Cleven et al., 2020). A systematic search in OVID, PubMed, and Web of Science databases was carried out. Longitudinal studies with more than 5 years of follow-up, conducted in samples of more than 500 participants, aged 18 years and older, and free of the respective conditions at baseline were included. PA could be leisure-time/ habitual PA, work-related PA, transportation-related PA, organized and unorganized PA. Overall, a favorable association between higher PA levels and a decreased risk of incident obesity, CHD and diabetes but not hypertension was observed (Cleven et al., 2020).

One conclusion from the review was, that no longitudinal study conducted in Germany was found (except for one cumulated analysis of selected European studies, Ekelund et al., 2012). However, health surveys/ longitudinal studies for adults in the context of PA and health exist in Germany (i.e. DEGS (Gößwald et al., 2013; Paprott et al., 2015); GEDA (Starker et al., 2022); Gesundheit zum Mitmachen (i.e. Woll, 1996)).

Excursus 'Gesundheit zum Mitmachen'

The *Gesundheit zum Mitmachen* study is an ongoing, community-based longitudinal cohort study that has been running over 29-years with six measurement points (1992, 1997, 2002, 2010, 2015, 2021), and aims at examining health, physical activity, and fitness of middle-aged and older adults (range: 33-86 years) residing in the city of Bad Schönborn in Germany (i.e. Tittlbach et al., 2017; Woll et al., 2004). The central aim of the study is to examine the inter-relationships of health, motor performance, and PA. Therefore, the study is based on integrative health theories from Antonovsky (1979, 1987) and Becker et al. (1994). Due to these theoretical foundations, an adapted version of the requirements and resources model modified by Woll (1996) is applied to verify the underlying estimations (please refer to Figure 6), assuming that individual external and internal risk factors and resources affect health on a continuum between health and disease.

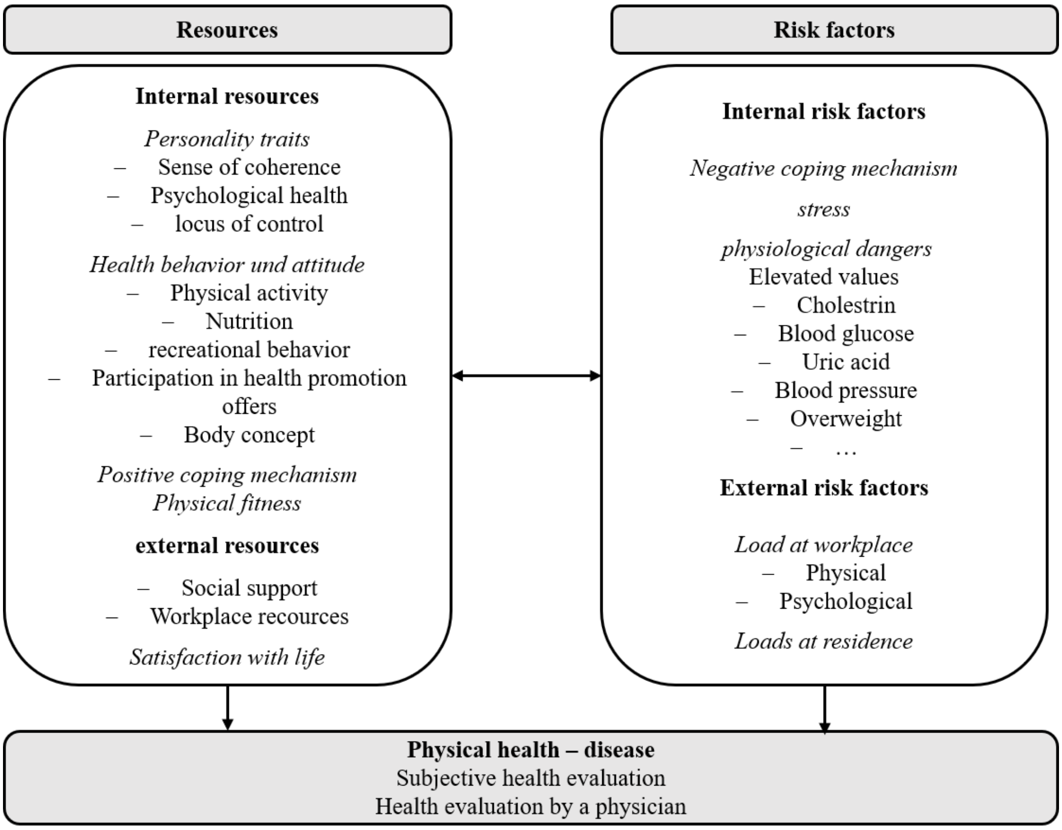


FIGURE 6: ADAPTED MODEL OF REQUIREMENTS AND RESOURCES (BASED ON WOLL, 1996)

Briefly, in *Gesundheit zum Mitmachen*, individuals residing in Bad Schönborn, Germany are randomly selected from the local residents' registration offices and invited to participate in the study.

Persons who participated in the study at least once are re-invited for every measurement point, and new samples of participants aged 33-37 years are included at each measurement point to prevent sample attrition. Participation in the study is voluntary and all participants provide written informed consent.

At each of the six measurements points, participants provide information about self-rated health status (i.e. with scales for the assessment of internal and external resources and risk factors), habitual and sports-related PA, and sociodemographic information through a self-reported questionnaire. All participants also undergo an objective health status examination conducted by a licensed physician, have a blood sample drawn, and undergo a motor fitness test.

By means of a self-reported questionnaire, participants answer questions about their PA behavior (general sports participation, sports-related, work-related, recreational PA). An index to quantify the amount of habitual PA (minutes per week) as indicator for recreational PA level (thus deliberately excluding sports activity participation) is then created as a sum index derived from participants‘ self-reported information about daily minutes of walking, biking for transportation, as well as working in the household and gardening (Woll et al., 2004). An index to examine the amount of sports-related PA per week is calculated from information provided by participants about frequency (i.e., number of weekly exercise sessions), duration (i.e., minutes per session), intensity (i.e., not very intense, moderately intense with some sweating, and highly intense with much sweating), and type of weekly sports-related PA (Woll et al., 2004). Furthermore, to consider the intensity level of the activity, every type of sport is assigned a specific MET-value (Ainsworth et al., 2011), and by multiplication with the time spent carrying out the respective activity, sports-related PA in MET-hours (METh) per week is calculated.

In addition to a detailed assessment of PA behavior, *Gesundheit zum Mitmachen* examines all relevant underlying risk factors of MetS (i.e. waist circumference, blood pressure, blood lipids, glucose levels) since 1992 at every measurement point (follow-up time 29 years) as assessed by self-report, as well as by evaluation from a licensed physician and results from blood draw (Woll et al., 2004).

The systematic review showed, that only few studies exist with a follow-up time longer than 20 years (i.e. Carlsson et al., 2013; Chomistek et al., 2016; Cohen et al., 2012; Elwood et al., 2013). However, those studies do not focus on new onset of MetS. Furthermore, results indicated, that only few studies reported results for change in PA behavior over time as independent variable (i.e. Cleven et al., 2020; Jefferis et al., 2014; Petersen et al., 2012), whereas most of the studies focus on a one-time measurement of PA (Cleven et al., 2020) to detect potential associations with new onset of diseases.

As stated above, however, PA behavior varies over time, and as NCDs and their respective risk factors also develop over a long period of time, change in PA behavior in longitudinal studies should be considered. Therefore, two studies were conducted (Publication II and III) in the setting of the population-based *Gesundheit zum Mitmachen study*. This led to the second research question:

Question 2: Is there an association between (change in) physical activity and incident metabolic syndrome in middle-aged adults in Germany?

In publication II, the longitudinal association between (change in) PA and the risk of incident MetS among middle-aged, community-dwelling adults was examined. In this analysis, 591 individuals (314 females; mean (SD) age, 43.8 (8.5) years) who were free of MetS at baseline and participated at least two times in the study were included. Habitual and sports-related PA was assessed by a self-reported questionnaire, and was considered as predictor variables. MetS was defined based on HDL-cholesterols, TG, BG, BP, and WC diagnosed by a physician and/ or determined by blood samples as stated above, and by self-reported questionnaires, and was considered as outcomes of interest for the analyses.

Therefore, to answer the research question, Cox proportional HRs and 95 % CI using regression analyses were calculated with adjustments for age, sex, and socio-economic status (Cleven et al., 2022). To consider time under observation in the models, and as each participant has a different follow-up time, time of study entry was set as baseline for each participant, respectively.

To control, whether the WHO recommended levels of PA are suitable for a risk reduction of MetS, cutoff-points according to the WHO recommendations were defined (World Health Organization, 2020). Furthermore, in addition to PA behavior at study entry, change in PA behavior was considered as well. Thus, PA behavior at study entry was compared to the PA behavior at the latest study visit. To this end, the same cut-off points as for baseline assessment were set and different groups were defined (i.e. stable active, starts activity, quits activity, stable inactive).

It was observed that four different sports-related PA measures were associated with a decreased risk of incident MetS, with risk reductions ranging between 29-38 %. This analysis also showed, that maintaining, starting or increasing sports-related PA is associated with a lower risk of incident MetS (Cleven et al., 2022).

Based on these results, in a next step, individual underlying risk factors of MetS were examined. Several studies are available that investigated the outcome of single risk factors of MetS (i.e. Carlsson et al., 2013; Ekelund et al., 2012; Medina et al., 2018). However, longitudinal studies reporting the association between variables of PA as predictor variables and individual risk factors of MetS as outcomes of interest are scarce. While it is important to focus on MetS itself (as done in Publication II), a potential association between PA and the risk of new onset of the respective individual risk factors of MetS should be considered as well (Research Question 3).

Question 3: Is there an association between (change in) physical activity and incident risk factors of metabolic syndrome in middle-aged adults in Germany?

To answer the third research question, the longitudinal associations between (change in) PA with the new onset of five risk factors of MetS among middle-aged adults were examined. In this analysis, 657 adults (mean age 44.1 (SD 8.6) years) who were free of the respective outcome at baseline were included. Levels of habitual PA and (change in) sports-related PA were assessed by a self-reported questionnaire, and considered as predictor variables. Incident elevated WC, elevated TG, reduced HDL, elevated BP, and elevated BG were assessed by physicians and/ or by blood samples, and by self-reported questionnaires, and were considered as outcomes of interest for the analyses. Cox proportional HR regressions and 95 % CI with adjustment for age, sex, and socio-economic status, and comorbidities at study entry related to the risk factors of MetS (i.e., elevated WC, reduced HDL, elevated TG, elevated BP, elevated BG), respectively, were calculated. Again, to consider time under observation in the models, and as each participant have a different follow-up times for each risk factor, time of study entry was set as baseline for each participant and each risk factor, respectively.

A similar approach as in publication II was followed with regard to variables on change in PA over time. Thus, to control, whether the WHO recommended levels of PA are suitable for a risk reduction of risk factors of MetS, cutoff-points according to the WHO-recommendation were defined (World Health Organization, 2020). Furthermore, in addition to PA behavior at study entry, change in PA behavior was considered as well. To this end, PA behavior at study entry was compared to the PA behavior at the latest study visit. Therefore, the same cut-off points as for baseline assessment were set and different groups were defined (i.e. stable active, starts activity, quits activity, stable inactive).

This analysis showed, that sports participation at baseline, in particular high sports-related PA levels at baseline were associated with a reduced risk of new onset of reduced HDL, but this was not true for habitual PA. Furthermore, starting and maintaining high levels of sports-related PA were associated with a reduced risk of onset of elevated WC, TG, BG, and reduced HDL, but not BP. Additionally, an elevated risk for the onset of BP was found as predicted by higher sports-related PA levels at baseline and by quitting sports-related PA from baseline to follow-up. In conclusion, this analysis showed that, PA at baseline, starting PA engagement, maintaining and increasing PA levels over time were associated with favorable metabolic health outcomes (Cleven et al., 2023).

2 THE ASSOCIATION BETWEEN PHYSICAL ACTIVITY WITH INCIDENT OBESITY, CORONARY HEART DISEASE, DIABETES AND HYPERTENSION IN ADULTS

Publication I: The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012

Slightly modified version of the published manuscript.

Cleven, L., Krell-Roesch, J., Nigg, C. R., & Woll, A. (2020). The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. *BMC public health*, *20*(1). 726. https://doi.org/10.1186/s12889-020-08715-4

2.1 ABSTRACT

Background: A growing body of studies that investigated the longitudinal association between physical activity (PA) and the outcome of incident obesity, coronary heart disease (CHD), diabetes and hypertension has become available in recent years. Thus, the purpose of this systematic review was to provide an update on the association between PA and onset of obesity, CHD, diabetes and hypertension in individuals aged ≥18 years who were free of the respective conditions at baseline.

Methods: We systematically searched OVID, PubMed, and Web of Science databases for pertinent literature published between January of 2012 and February of 2019. To ensure that conclusions are based on high quality evidence, we only included longitudinal studies conducted in samples of ≥500 participants and with ≥5 years of follow-up.

Result: The search yielded 8929 records of which 26 were included in this review. Three studies were conducted on the outcome of incident obesity, eight on incident CHD, nine on incident diabetes, four on incident hypertension, one on the outcome of both diabetes and hypertension, and one on the outcome of CHD, diabetes and hypertension. Overall, there was an association between PA and lower risk of incident obesity, CHD and diabetes, but not hypertension. Higher levels or amount of PA were associated with a reduced risk of new onset of the respective diseases in 20 studies (77 %). Whereas four studies reported an elevated risk of incidence of diseases with lower PA levels (15 %). PA was not associated with incidence of diseases in two studies (8 %).

Conclusion: Higher levels of PA are likely associated with a lower risk of becoming obese, develop CHD or diabetes. These findings replicate and strengthen conclusions from earlier reviews underlining the importance of promoting PA in adults. The associations between PA and incident hypertension were less consistent. More research, particularly using prospective cohort designs in large population-based samples, is needed to further untangle the association between PA and incident hypertension.

Trail registration: CRD42019124474 (PROSPERO Protocol registration). Date of registration in PROSPERO 27 February 2019.

Keywords: Physical activity, Obesity, Coronary heart disease, Diabetes, Hypertension, Adults, Longitudinal study, Cohort study

2.2 Background

The World Health Organization (WHO) identified noncommunicable diseases (NCDs), such as diabetes mellitus or cardiovascular diseases to be a major threat to economies and societies (World Health Organization, 2014). NCDs are implicated in 73 % of all global deaths in 2017, with 28.8 million deaths attributed to risk factors like high blood pressure, high blood glucose, or high body mass index (BMI) (The Lancet, 2018). Furthermore, NCDs are forecasted to account for 81 % of all global deaths in 2040 (Foreman et al., 2018).

NCDs usually develop over a long time period and may be impacted by an individual's health behaviors (Arts et al., 2014). As such, many NCDs may be preventable by decreasing metabolic risk factors such as hypertension, overweight and obesity, or hyperglycemia, as well as by decreasing behavioral risk factors like tobacco or alcohol use, an unhealthy diet, and physical inactivity (Forouzanfar et al., 2016; World Health Organization, 2014).

A growing body of research suggests that high levels of physical activity (PA) may have a protective effect on various health conditions including but not limited to overweight and obesity (Madjd et al., 2016), coronary heart disease (CHD) (Colditz et al., 2016; Hambrecht et al., 2000), type 2 diabetes mellitus (Church et al., 2010; Johannsen et al., 2013), hypertension (Nelson et al., 1986; Stewart et al., 2005), and hyperglycemia (Avery & Walker, 2001; Fritz & Rosenqvist, 2001). In addition, several longitudinal studies have become available that examine the association between PA and new onset of NCDs (Kannel et al., 1986; Leon, 1987; Paffenbarger et al., 1970; Reiner et al., 2013; Sesso et al., 2000; Sherman et al., 1994).

The current systematic review presents an update of a previously published review by our group (Reiner et al., 2013), that examined the long-term effects of PA on type 2 Diabetes mellitus, CHD, overweight/ obesity and dementia by including studies published before 2012. Given the high significance of this topic and since we expected a substantial amount of relevant studies published after 2012, we provide an updated review of longitudinal studies on the association between PA and incident obesity, CHD, diabetes and hypertension over the past 7 years. Hypertension has been added to the current review as it is widely regarded as a major risk factor for several NCDs (World Health Organization, 2013).

2.3 METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (Moher et al., 2009). The protocol was registered in the PROSPERO register of systematic reviews (CRD42019124474).

2.3.1 SEARCH STRATEGY

Pertinent articles published between January of 2012 and February of 2019 were searched in electronic databases (PubMed, Web of Science and EMBASE by OVID) by applying a combination of one or more of the following search terms: “longitudinal and/ or long-term”; “physical activity/ exercise”; “adult”; “overweight and/ or obesity”, “coronary heart disease and/ or coronary artery disease and/ or ischemic disease”, “diabetes mellitus and/ or diabetes type 2”, “hypertension and/ or blood pressure”. Both titles and abstracts were searched. After identification of studies, their bibliographies were searched manually to identify additional relevant studies.

2.3.2 STUDY INCLUSION & EXCLUSION CRITERIA

We defined the following inclusion criteria for this systematic review: (1) Longitudinal, i.e. prospective cohort study design; (2) Studies reporting the association between PA and new onset of obesity, CHD, type 2 diabetes mellitus and/ or hypertension; (3) Studies providing information on the assessment of PA (predictor variable).

PA could be leisure-time/ habitual PA, work-related PA, transportation related PA, organized and unorganized PA, etc.; (4) Only studies with ≥5 years of follow-up were included to allow for a meaningful conclusion on the longitudinal association between PA and selected outcomes of interest; (5) Studies with males and females aged ≥18 years, that were free of the diseases of interest at baseline; (6) Studies with more than 500 participants were included, to improve the probability to capture a substantial amount of incidence cases; and (7) articles written in English.

Excluded from this review were (1) studies investigating the effect of a specific PA intervention, as well as (2) clinical trials, cross-sectional studies, systematic reviews and meta-analyses.

2.3.3 Screening & data extraction

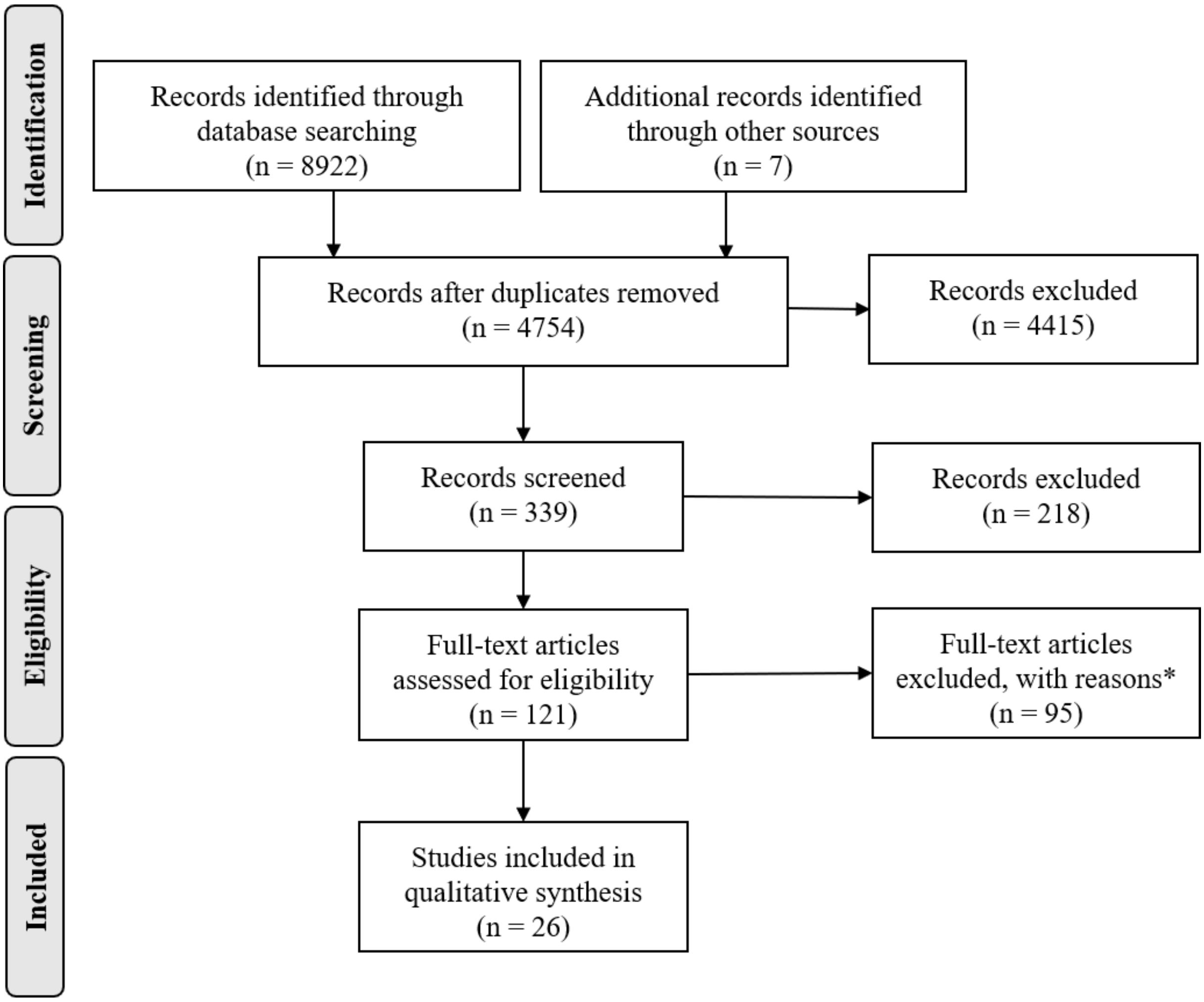
All pertinent studies detected after searching the electronic databases were imported to a reference manager software (Citavi 6) and duplicates were removed. The study selection process was divided into three phases. Two independent reviewers (LC & JKR) screened the titles of the articles, followed by the abstracts, and finally the full-texts based on the inclusion criteria. All studies meeting the eligibility criteria were included in this review. Disagreement was resolved by consensus or by consulting a third author (CN). The following information was extracted by one reviewer (LC): first author's name, publication year, study design, study setting, sample size, follow-up time, participant characteristics (e.g. age, sex, BMI) at baseline, assessment and type of PA (e.g. type, duration, intensity), assessment and type of outcomes of interest (i.e. obesity, CHD, diabetes and hypertension), and main results/ findings of the study (e.g. hazard ratios, relative risk). Extracted data were verified by another author (JKR).

2.3.4 Quality assessment and risk of bias

The quality of included studies was evaluated independently by two authors (LC & JKR) using the 22-item Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement version 4 (Elm et al., 2007). Similarly, potential risk of bias of each study included in this systematic review was assessed through the Tool to Assess Risk of Bias in Cohort Studies (*Tool to Assess Risk of Bias in Cohort Studies*, 2022) by the same authors (LC & JKR). Any discrepancies between the two reviewers were resolved by discussion or by consulting a third reviewer (CN).

2.4 Results

Overall, we identified 8929 articles, of which 8903 articles were excluded as they did not meet the inclusion criteria as described above. The reader is referred to Figure 7 for a flow chart summarizing the search process and number of studies at each step. Twenty-six studies were included in this review with a combined N of 1,145,298 participants, and follow-up times ranging between 5 and 34 years. Three articles examined the association between PA and incident obesity (Bell et al., 2014; Montgomerie et al., 2014; Pavey et al., 2016), eight studies examined the association between PA and incident CHD (Chomistek et al., 2016; Delaney et al., 2013; Ferrario et al., 2018; Jefferis et al., 2014; Koolhaas et al., 2016; Petersen et al., 2012; Soares-Miranda et al., 2016; Tikkanen et al., 2018), nine studies examined the association between PA and incident diabetes (Carlsson et al., 2013; Ekelund et al., 2012; Elwood et al., 2013; Grøntved et al., 2014; Hjerkind et al., 2017; Jefferis et al., 2012; Koloverou et al., 2018; Mehlig et al., 2014; Shi et al., 2013), and four studies examined the association between PA and incident hypertension (Cohen et al., 2012; Lu et al., 2015; Pavey et al., 2013; Stenehjem et al., 2018). In addition, one study reported the association between both PA and diabetes as well as PA and hypertension (Medina et al., 2018), and another study reported the association between PA and CHD, diabetes, and hypertension (Williams & Thompson, 2013).



* = main reasons for exclusion of studies (n= 35 other outcomes of interest; n= 24 other definition of PA; n= 10 other study designs; n= 6 follow-up time < 5 years; n= 20 other reasons)

Figure 7: Flow chart (based on Moher et al., 2009)

2.4.1 Association between PA and obesity

The studies included in this review showed an overall association between higher PA and lower risk of incident obesity. Two out of three studies reported a reduced risk of becoming obese for individuals with high PA levels as compared to low PA (Bell et al., 2014; Pavey et al., 2016). One study showed an elevated risk (142 %) of becoming obese for persons who were physically inactive (Montgomerie et al., 2014). The characteristics of the included studies are summarized in Table 2.

Table 2: Overview of longitudinal studies on the association between PA and the outcome of obesity (BMI ≥ 30 kg/m2)

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Bell et al. (2014)	UK, Whitehall II study	N = 3670, 73% male, 55.5 ± 6.0 years	10 years; Baseline 1997-1999 Follow-up: 2002-2004, 2007-2009	Self-reported, duration MVPA (h/wk): – Low: 0–1.5 – Intermediate: 1.56–4.25 – High: 4.27–20.56	Incident obesity	OR [95% CI], low level PA as reference#1: – High level PA 0.64 [0.44, 0.93] after 5 years – High level PA 0.63 [0.45, 0.88] after 10 years
Montgomerie et al. (2014)	Australia	N = 1521, 50.6% male, age 44.6 ± 16.22 years	2898.9±402.29 days Baseline: 1999-2003, follow-up: 2004-2006, 2008-2010	Self-reported, score: frequency x time per session x intensity; – Inactive: <100 sedentary, 100-1600 low – Active: 1600-3200 moderate, >3200 high	Incident obesity	RR [95% CI]: Association between physical inactivity & incident obesity#2: – 1.42 [1.03, 1.95] p= 0.030
Pavey et al. (2016)	Australia	N = 2735 women, 24.6 (20.6-28.5) years	12 years Baseline: 2000 Follow-up: 2012	Self-reported, score (MET-min/wk): – Very low (<250) – Low (250 to <500) – Active (500 to <1000) – Very active (>1000)	Change in BMI category	OR [95% CI], increasing cumulative PA with very low activity as reference#3: – Transition to obesity: 0.73 [0.59, 0.90], p<.05 OR [95% CI], very high cumulative PA with very low activity as reference – Transition to obesity 0.52 [0.30, 0.92], p<.05

Abbreviation: BMI – Body Mass Index, CI – confidence interval, h – hour, Met – metabolic equivalent, min – minutes, MVPA – moderate-to-vigorous physical activity, N – number of participants, OR – odds ratio, p – p-value, PA – physical activity, RR – relative risk, SD – Standard deviation, wk – week

#1 Model adjusted for age, sex, ethnicity; #2 Model adjusted for age, sex, chronic conditions (diabetes, asthma, chronic obstructive pulmonary disease, cardiovascular disease and mental health); #3 Model adjusted for educational level, area of residence, number of children, occupation, work time walking, work time in heavy labor, smoking status, alcohol consumption, energy intake, dieting, oral contraceptive pill use, number of chronic conditions

2.4.2 *Association between PA and CHD*

Overall, there was an association between higher levels or amount of PA and a decreased risk of incident CHD. Seven out of nine studies reported a reduced risk of new onset of CHD with increasing PA levels as compared to low or no PA (Chomistek et al., 2016; Koolhaas et al., 2016; Petersen et al., 2012; Soares-Miranda et al., 2016; Tikkanen et al., 2018), whereas one study revealed an association between PA and decreased CHD risk only for vigorous intensity PA (Delaney et al., 2013). One study did not find a significant association for occupational PA and CHD risk (Ferrario et al., 2018). Two out of nine studies examined the impact of change in PA levels over time as predictor variable and failed to detect a significant association with incident CHD (Jefferis et al., 2014; Petersen et al., 2012). Please refer to Table 3 for a summary of studies on PA and incident CHD.

TABLE 3: OVERVIEW OF LONGITUDINAL STUDIES ON THE ASSOCIATION BETWEEN PA AND THE OUTCOME OF CHD

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Chomistek et al. (2016)	USA, Nurses' Health Study II (NHSII)	N = 97230 women, 36.6 ± 4.6 years	20 years Baseline: 1991 Follow-up: 2011	Self-reported leisure time PA (MET-h/wk, in quintiles) – <1 – 1-5.9 – 6-14.9 – 15-29.9 – ≥30	Incident CHD (nonfatal MI, fatal CHD)	HR [95% CI] of CHD event for total PA°1: – <1: 1.0 (reference) – 1-5.9: 0.86 [0.68, 1.08] – 6-14.9: 0.66 [0.52, 0.84] – 15-29.9: 0.48 [0.36, 0.63] – ≥30: 0.53 [0.41, 0.70] Similarly, increasing MET-h/wk were associated with a decreased risk of incident CHD when looking at moderate-intensity PA only, as well as looking at vigorous-intensity PA only.
Delaney et al. (2013)	USA, Multi-Ethnic Study of Atherosclerosis (MESA)	N = 5656, 47.4% male, 61.3 ± 9.9 years, BMI 28.3 ± 5.4 kg/m^2	5 years Baseline 2000-2002 Follow-up: 2005-2007	Self-reported PA (total min/d, total MET-min/d)	Incident coronary artery calcification (CAC)	RR [95% CI] of PA and incident CAC°2: – Vigorous activity: 0.97 [0.94, 1.00], p=0.048 No association between intentional, sedentary, MVPA and conditioning PA and incident CAC.
Ferrario et al. (2018)	Italy, MONICA, PAMELA, SEMM	N = 3574 men, 25-64 years	Median 14 years (IQR 12.9–15.9) Baseline: 1989-1996 Follow-up: 2008	Self-reported, OPA score 1-5 (tertiles, cut-offs at 2.5, 3.125) SpPA index (min/wk of moderate or VPA based on METs of task) – Poor: 0 – Intermediate: 1–149 MPA or 1–74 VPA or 1–149 MPA plus VPA – Recommended: ≥150 MPA or ≥75 VPA or ≥150 MPA plus VPA	Incident CHD (first acute coronary event as MI, acute coronary syndrome or coronary revascularization)	HR [95% CI] of first CHD event (fatal or non-fatal) by OPA group°3: – Low: 1.66 [1.06, 2.59] – Intermediate: 1.0 (reference) – High: 1.18 [0.72, 1.94] HR [95% CI] of first CHD event (fatal or non-fatal) by SpPA group°3: – Poor: 1.0 (reference) – Intermediate: 0.81 [0.50, 1.32] – Recommended: 0.58 [0.30, 1.12]

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Jefferis et al. (2014)	UK, British Regional Heart Study	N = 3320 men, 68.3 ± 5.4 years	Median 11 years Baseline 1998-2000 Follow-up: 2010	Self-reported usual PA (score) – Inactive (0-2) – Occasional (3-5) – Light (6-8) – Moderate (9-12) – Moderately vigorous (13-20) – Vigorous (>21) Change in PA (1996-2000) – Always inactive – Became inactive – Became active – Always active	Incident CHD (First fatal or nonfatal MI events, ICD-9 Code 410-414, ICD-10 Code I21-I23, I252)	HR [95% CI] of first CHD event (fatal or non-fatal) by PA group°4: – None: 1.0 (reference) – Occasional: 0.52 [0.34, 0.79] – Light: 0.47 [0.30, 0.74] – Moderate: 0.51 [0.32, 0.82] – Moderately vigorous and vigorous: 0.44 [0.29, 0.65] $p = 0.004$ HR [95% CI] of first CHD event (fatal or non-fatal) by change in PA group: Model 1°4: – Always inactive: 1.0 (reference) – Became inactive: 0.87 [0.53, 1.45] – Became active: 0.86 [0.55, 1.35] – Always active: 0.73 [0.53, 1.02]
Koolhaas et al. (2016)	Netherlands, The Rotterdam Study	N = 5901, median age 67 years	15 years Baseline 1997-2001 Follow-up: 2012	Self-reported PA, tertiles (median (range) MET-h/wk in total PA) – Tertiles 1: 42.0 (≤61.4) ≙ 1.5h/d at 4 METs – Tertiles 2: 77.5 (61.5-96.9) ≙ 2.8h/d at 4 METs – Tertiles 3: 126.7 (≥97.0) ≙ 4.5h/d at 4 METs	Incident CHD (fatal or nonfatal MI, surgical/ percutaneous coronary revascularization procedure)	HR [95% CI] Total PA and risk of incident CHD event°5: – Tertile 1: 1.0 (reference) – Tertile 2: 0.76 [0.63, 0.92] – Tertile 3:0.69 [0.57, 0.84] Per 10 MET-h/wk: 0.96 [0.94, 0.98]. p overall = <0.001.

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Petersen et al. (2012)	Denmark, Copenhagen City Heart Study	N = 10443, 57% female, median age 58 years	Baseline 1976-78 Follow-up: 1981-1983, 2008	Self-reported leisure-time PA – Sedentary – Light – Moderate – Vigorous Change in PA categories (1976/78-1981/83) – -2/-3 categories – -1 category – 0 (stable) – +1 category – +2/+3 categories	Incident CHD fatal and non-fatal cases (MI: ICD-8 Code 410, ICD-10 Code I21-22; IHD: ICD-8 Code 410-414, ICD-10 Code I20-25)	HR [95% CI] of IHD by PA change[°6]: Women | Men – -2: 1.60 [1.02, 2.32] | 1.33 [0.97, 1.83] – -1: 1.28 [1.10, 1.49] | 1.12 [0.96, 1.31] – 0: 1.0 (reference) – 1: 0.97 [0.85, 1.12] | 1.09 [0.96, 1.25] – 2: 1.01 [0.75, 1.38] | 1.16 [0.89, 1.51] HR [95% CI] of MI by PA change[°6]: Women | Men – -2: 1.56 [0.89, 2.75] | 1.74 [1.17, 2.60] – -1: 1.30 [1.03, 1.65] | 1.13 [0.91, 1.39] – 0: 1 (reference) – 1: 0.98 [0.79, 1.22] | 1.14 [0.95, 1.36] – 2: 1.08 [0.67, 1.75] | 1.30 [0.92, 1.84]
Soares-Miranda et al. (2016)	USA	N = 4207, 39% males, 72.5 ± 5.5 years	10 years Baseline: 1989 Follow-up: 1999	Self-reported leisure time PA (kcal/wk), Exercise intensity: – None – Low – Moderate – High	Incident CHD (fatal & nonfatal MI & CHD death)	HR [95% CI] for exercise intensity[°7], none as reference: – Low: 0.56 [0.43, 0.72], p <0.001 – Moderate: 0.53 [0.41, 0.69], p <0.001 – High: 0.47 [0.32, 0.69], p <0.001
Tikkanen et al. (2018)	UK	N = 502635, 54% female, 56.5 ± 8.1 years	Median 6.1 years Baseline: 2006-10 Follow-up: 2015-2016	Self-reported (MET-h/wk)	Incident CHD (ICD-9 Code 410-411, ICD-10 Code I20.0, I21, I22)	HR [95% CI] association CHD and PA level[°8]: – 0.95 [0.93, 0.97], p <0.001
Williams & Thompson (2012)	USA	N = 47921	Median 6.2 years Baseline: 1998-1999 Follow-up: 2006	Self-reported PA METh/d – Light – Moderate – Vigorous	Incident CHD (MI, CABG, percutaneous coronary intervention, and angina pectoris)	Greater METh/d is associated with lower risk of incident CHD HR [95% CI][°9] – Running: 0.955 [0.91, 1.00] – Walking: 0.907 [0.839, 0.98] – Other vigorous: 0.99 [0.966, 1.02] – Other moderate: 0.98 [0.927, 1.04] – Other light: 0.98 [0.807, 1.197]

Abbreviation: BMI – Body Mass Index, CABG – coronary artery bypass graphs, CAC – coronary artery calcification, CHD – coronary heart disease, CI – confidence interval, d – day, h – hour, HDL – high-density lipoprotein, HR – hazard ratio, ICD – International Classification of Diseases, IHD – ischemic heart disease, IQR – interquartile range, kcal - kilocalories, MET – metabolic equivalent, MI – Myocardial Infarction, min – minutes, MPA – moderate physical activity, MVPA – moderate to vigorous physical intensity, N – number of participants, OPA – occupational physical activity, p – p-value, PA – physical activity, RR – relative risk, SpPA – sport physical activity, VPA – vigorous physical activity, wk – week

°[1] Model adjusted for age; °[2] Model adjusted for age, sex, ethnicity, BMI, pack years of smoking, family history of MI, hypertension, dyslipidemia, diabetes, education, alcohol use, current smoking status, education, income, health insurance status; °[3]: Model adjusted for age, cohort, educational level, OPA and SpPA; °[4] Model adjusted for age and region; °[5] Model adjusted for age and sex; °[6] Model adjusted for physical activity level in 1976–1978, age, education, smoking habits, alcohol consumption, BMI, diabetes, cholesterol, blood pressure lowering therapy in 1981–1983; °[7] Model adjusted for age, sex, race, education, income, clinical sites, smoking, BMI; °[8] Model adjusted for age, sex, region; °[9] Model adjusted for baseline age (age, age2), sex, race, education, smoking, intakes of red meat, fruit, alcohol

2.4.3 *Association between PA and diabetes*

The studies included in this review provide evidence of an association between increasing PA levels and a decreased risk of incident diabetes. Nine out of 11 studies reported a gradual inverse association between increasing PA levels with up to high/ vigorous-intensity and a decreased risk of incident diabetes (Carlsson et al., 2013; Ekelund et al., 2012; Elwood et al., 2013; Grøntved et al., 2014; Hjerkind et al., 2017; Jefferis et al., 2012; Koloverou et al., 2018; Shi et al., 2013; Williams & Thompson, 2013), whereas one study revealed an association only between moderate intensity PA and reduced diabetes risk (Koloverou et al., 2018). Two out of 11 studies reported an increased risk of incident diabetes (179 and 145 %, respectively) for participants engaging in low amount of leisure time PA as compared to the highly active reference group (Medina et al., 2018; Mehlig et al., 2014). For a summary of included studies on the association between PA and diabetes please refer to Table 4.

TABLE 4: OVERVIEW OF LONGITUDINAL STUDIES ON THE ASSOCIATION BETWEEN PA AND THE OUTCOME OF DIABETES

Author	**Country**	**Characteristics**	**Follow-up time**	**Predictor variable: Physical activity**	**Outcome of interest**	**Main results**
Carlsson et al. (2013)	Sweden (Swedish Twin Registry)	N = 23539	Baseline: 1967-1972 Follow-up: 1998-2002	Self-reported leisure time PA – Low – Moderate – high	Incident type 2 diabetes	Risk of type 2 diabetes decreased with PA: HR [95% CI] – Low: 1.0 (reference) – Moderate: 0.77 [0.61, 0.96] – High: 0.53 [0.37, 0.75]
Elwood et al. (2013)	UK (Caerphilly Prospective Study CaPS)	N = 2235 men, 45-59 years	30 years Baseline: 1979-1983 Follow-up: 1984-1988, 1989-1993, 1993-1997, 2009	Self-reported PA	Incident diabetes (self-reported)	OR [95% CI] for regular activity and incident diabetes – 0.63 [0.46, 0.85]
Grøntved et al. (2014)	USA (Nurses' Health Study NHS I and II)	N = 99316 women	8 years Baseline (NHS I): 2000 Baseline (NHS II): 2001 Follow-up (NHS I): 2008 Follow-up (NHS II): 2009	Self-reported PA (time spent on resistance exercise per week, lower intensity muscular conditioning exercises (yoga, stretching, toning), aerobic MVPA) – None – 1-29 min/wk – 30-59 min/wk – 60-50 min/wk – > 150 min/wk	Incident diabetes (self-report confirmed using standardized criteria; validated in sub-sample through medical chart review)	RR [95% CI] for incident diabetes for aerobic MVPA – None: 1.0 (reference) – 1-29 min: 0.83 [0.74, 0.92] – 30-59 min: 0.73 [0.65, 0.82] – 60-150 min: 0.66 [0.60, 0.73] – ≥ 150 min: 0.46 [0.41, 0.50] – Trend: $p < 0.001$ Engaging in at least 150 min/wk of aerobic MVPA and at least 60 min/wk of muscle-strengthening activities was significantly associated with lower risk of incident diabetes compared with being inactive (pooled RR = 0.33 [0.29, 0.38]).
Hjerkind et al. (2017)	Norway (Nord-Trøndelag Health Study)	N = 38413 with information on PA, 47% males	11 years Baseline: 1984-1986 Follow-up: 1995-1997	Self-reported leisure time PA – Low – Medium – High	Incident diabetes (self-reported; validated through medical record)	Risk of diabetes decreased with PA[*1]: RR [95% CI] Women | Men: – Low: 1.0 (reference) – Medium: 0.81 [0.65, 1.00] | 0.80 [0.66, 0.98] – High: 0.76 [0.61, 0.95] | 0.65 [0.51, 0.84] $p = 0.01$ | $p < 0.01$ Gradual inverse association between frequency, duration, intensity and risk of incident diabetes for males Gradual inverse association between frequency, intensity and risk of incident diabetes for females

Author	**Country**	**Characteristics**	**Follow-up time**	**Predictor variable: Physical activity**	**Outcome of interest**	**Main results**
Ekelund et al. (2012)	8 European countries (EPIC–InterAct Study)	N = 11669 men, 15695 women N = 15934 subcohort (6009 men, 9925 women)	Median 12.3 years Baseline: 1991 Follow-up: 2007	Self-reported PA (OPA, LTPA) – Inactive – Moderately inactive – Moderately active – Active	Incident diabetes	A one level difference in physical activity (e.g. between inactive and moderately inactive) was associated with a 13% relative reduction in risk of incident diabetes in males (HR [95% CI] 0.87 [0.80, 0.94]) and 7% risk reduction in females (0.93 [0.89, 0.98])[*2] Increased risk of incident diabetes associated with lower levels of physical activity evident across BMI strata in both sexes, with the exception of obese women
Jefferis et al. (2012)	UK	N = 3012 men, 68.3 years	Median 7.1 years Baseline: 1996, 1998-2000 Follow-up: 2006	Self-reported PA – None – Occasional – Light – Moderate – Moderately vigorous – Vigorous	Incident type 2 diabetes (self-report included after validation through medical record)	Risk of diabetes decreased with PA: Dose-response association[*3]: HR [95% CI] – None: 1.0 (reference) – Occasional: 0.54 [0.31, 0.96] – Light: 0.34 [0.18, 0.65] – Moderate: 0.33 [0.17, 0.65] – moderately vigorous: 0.32 [0.16, 0.61] – vigorous: 0.26 [0.13, 0.53] $p < 0.01$ Taking up at least moderate intensity PA also associated with lower risk of diabetes.
Koloverou et al. (2017)	Greece (Attica Study)	N = 1485, 49% males	10 years Baseline: 2001-2002 Follow-up: 2011-2012	Self-reported PA (MET-min/wk) – Very low ≤150 – Low = 150-330 – Moderate = 331-1484 – High ≥1484	Incident diabetes (measured in biological sample or self-reported)	Moderate intensity PA associated with lower risk of incident diabetes[*4]: OR [95% CI] – Very low: 1.0 (reference) – Low: 0.77 [0.41, 1.49] – Moderate: 0.47 [0.24, 0.93] – High: 1.04 [0.59, 1.82]
Medina et al. (2018)	Mexico (Mexico City Diabetes Study)	N = 1883, median 45 years (IQR 39- 52); 42.7% males	Median 14.4 person years Baseline: 1989-1990 Follow-up: 1993-1994, 1997-1998, 2008-2009	Self-reported PA (occupational, leisure, total PA in MET-min/wk of MVPA) – 1 = <1 – 2 = 1-599.9 – 3 = 600-1199.9 – 4 = ≥ 1200	Incident type 2 diabetes (measured, self-reported, taking medication)	Participants with leisure PA <1 MET-min/wk had increased risk of incident diabetes (HR 1.45 [95% CI: 1.10, 1.92]) as compared to reference group (≥ 1200 MET-min/wk of MVPA; $p = 0.008$)[*5] No association between occupational and total PA and diabetes risk.

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Mehlig et al. (2014)	Sweden	N = 1448 women, 38-60 years	34 years Baseline: 1968-1969 Follow-up: 1974-1975, 1980-1981, 1992-1993, 2000-2001, 2000	Self-reported LTPA – Almost inactive: low LTPA – Some PA at least 4 h/wk – Regular exercise – Regular training and competitive sports	Incident diabetes	LTPA is associated with an elevated risk in incident diabetes, HR [95% CI][*6] – Non-obese, active: 1.0 (reference) – Non-obese, inactive: 1.79 [1.15, 2.79] – Obese, active: 2.43 [1.44, 4.09] – Obese, inactive: 11.7 [6.28, 21.8]
Shi et al. (2013)	China	N = 51464 men, 54.1 ± 9.3 years	Median 5.4 years Baseline: 2002-2006 Follow-up: 2004-2008, 2008-2011	Self-reported PA MET level (in quintiles) – Q1 < 4.3 – Q2 4.3-6.5 – Q3 6.5-8.9 – Q4 8.9-12.1 – Q5 ≥ 12.1	Incident diabetes (self-reported)	Total PA is associated with a reduced risk in incident diabetes, HR [95% CI] for MET level[*7] – Q1: 1.0 (reference) – Q2: 0.84 [0.72, 0.99] – Q3: 0.72 [0.61, 0.85] – Q4: 0.66 [0.55, 0.78] – Q5: 0.65 [0.54, 0.77]
Williams & Thompson (2012)	USA	N = 48116	Median 6.2 years Baseline: 1998-1999 Follow-up: 2006	Self-reported PA METh/d – Light – Moderate – Vigorous	Incident diabetes	Greater METh/d is associated with lower risk of incident Diabetes HR [95% CI][*8] – Running: 0.879 [0.83, 0.929] – Walking: 0.877 [0.82, 0.93] – Other vigorous: 0.98 [0.95, 1.007] – Other moderate: 0.969 [0.908, 1.02] – Other light: 0.99 [0.736, 1.12]

Abbreviation: BP - CI – confidence interval, d – day, h – hour, HR – hazard ratio, IQR – interquartile range, LTPA – leisure time physical activity, MET – metabolic equivalent, min – minutes, MVPA – moderate to vigorous physical activity, N – number of participants, OPA - occupational physical activity, OR – odds ratio, PA – physical activity, RR – relative risk, wk – week

[*1]: Model adjusted for age; education, alcohol frequency in the past 2 weeks, smoking, blood pressure medication use, prevalent cardiovascular disease, BMI, PA summary score; *[2] Model adjusted for study center, education, smoking status, alcohol consumption, energy intake, BMI; [*3] Model adjusted for age & region; [*4] Model adjusted for age, sex, family history of diabetes, hypertension, hypercholesterolemia, smoking status, education, physical activity, waist circumference, adherence to the Mediterranean diet, fasting glucose, triglycerides; [*5] Model adjusted for sex, age, education levels, marital status, current smoking, alcohol intake, total energy intake, parent history of diabetes, sleeping hours, leisure/working MET-min/wk; *[6] Model adjusted for baseline covariates age, education, smoking, consumption of alcohol, triglycerides, hypertension, parental history of diabetes (diabetes only); [*7] Model adjusted for age at interview, energy intake, smoking, alcohol consumption, education level, occupation, income level, hypertension, family history of diabetes; [*8] Model adjusted for baseline age (age, age2), sex, race, education, smoking, intakes of red meat, fruit, alcohol, preexisting CHD at baseline

2.4.4 Association between PA and hypertension

Overall, there was no consistent association between PA and incident hypertension. Three out of six studies reported a gradual inverse association between PA levels (running and walking, moderate and moderate-vigorous PA) and incident hypertension (Cohen et al., 2012; Pavey et al., 2013; Williams & Thompson, 2013), whereas one study found an association only for a specific age group (51-60 years) (Cohen et al., 2012). Two out of six studies found no significant association between PA and incident hypertension (Lu et al., 2015; Stenehjem et al., 2018). One out of six studies reported an increased risk of incident hypertension (137 %) for persons with low leisure time PA as compared to the highly active reference group (Medina et al., 2018). Please refer to Table 5 for an overview of included studies.

TABLE 5: OVERVIEW OF LONGITUDINAL STUDIES ON THE ASSOCIATION BETWEEN PA AND THE OUTCOME OF HYPERTENSION

Author	Country	Characteristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Cohen et al. (2012)	USA (Nurses' Health Study I cohort)	N = 78590 women; 49 years (IQR 44-56)	20 years Baseline: 1984 Follow-up: 2004	Self-reported PA METs/wk for vigorous exercise in quintiles (Q1-5)	Incident hypertension (self-reported; validated in NHS I cohort)	Association between PA and incident hypertension varies by age (p-value for interaction < 0.001). HR [95% CI] lowest for PA Q5 as compared to Q1. – Age ≥ 50: Q1 1.0 (reference); Q2 1.00 [0.91, 1.11]; Q3 1.03 [0.94, 1.14]; Q4 1.01 [0.91, 1.12]; Q5 0.87 [0.78, 0.97] – Age 51-60: Q1 1.0 (reference); Q2 0.94 [0.88, 1.00]; Q3 0.94 [0.88, 1.00]; Q4 0.91 [0.85, 0.97]; Q5 0.86 [0.80, 0.92] – Age ≥ 61: Q1 1.0 (reference); Q2 1.03 [0.97, 1.09]; Q3 0.98 [0.93, 1.04]; Q4 0.99 [0.93, 1.05]; Q5 0.95 [0.90, 1.01]
Lu et al. (2015)	China	N = 1009, 35.48 ± 0.19 years, 63.4% males	Median 4.7 years Baseline: 2004 Follow-up: 2012	Self-reported PA – Frequent – Occasional – Everyday	Incident hypertension	No significant association between PA and risk of hypertension[+1]: HR [95% CI] – Occasional: 0.74 [0.40, 1.39] – Frequent: 0.96 [0.51, 1.83] – Everyday: 1.0 (reference)
Medina et al. (2018)	Mexico (Mexico City Diabetes Study)	N = 1541, median 45 (IQR 39-52) years; 45.1% males	Median 11.8 years Baseline: 1989-1990 Follow-up: 1993-1994, 1997-1998, 2008-2009	Self-reported PA (occupational, leisure, total activity in MET-min/wk of MVPA) – 1 = <1 – 2 = 1-599.9 – 3 = 600-1199.9 – 4 = ≥ 1200	Incident hypertension (measured by study team)	Participants with <1 MET-min/wk of leisure (HR 1.37 [95% CI 1.07, 1.75], p = 0.015) or occupational MVPA (HR 1.52 [1.17, 1.97], p = 0.001) had increased risk of hypertension as compared to reference group (≥ 1200 MET-min/wk)[+2] No association was observed between total PA and hypertension.

Author	Country	Charac-teristics	Follow-up time	Predictor variable: Physical activity	Outcome of interest	Main results
Pavey et al. (2013)	Australia (Australian Longitudinal Study on Women's Health)	N = 11285 women, mean age 49.5 years	Baseline: 1998 Follow-up: 2001, 2004, 2007, 2010	Self-reported PA (MET-min/wk) – None – >0-<250 – 250-<500 – 500-<1000 – 1000-<1500 – 1500-<2000 – >2000 – Inactive – Moderate (MPA) – Moderate and vigorous activity (MVPA)	Occurrence of hypertension (self-reported)	OR [95% CI] for hypertension declined with increasing PA volume; decline slightly greater in MVPA than MPA group MPA[+3] | MVPA[+3]: – None: 1.0 (reference) – >0-<250: 0.92 [0.83, 1.02] | 0.87 [0.63, 1.04] – 250-<500: 0.90 [0.81, 1.00] | N.A. – 500-<1000: 0.82 [0.75, 0.91] | 0.73 [0.62, 0.86] – 1000-<1500: 0.74 [0.66, 0.82] | 0.65 [0.55, 0.76] – 1500-<2000: 0.78 [0.68, 0.90] | 0.63 [0.54, 0.74] – >2000: 0.80 [0.70, 0.93] | 0.56 [0.49, 0.64]
Stenehjem et al. (2018)	Norway (Nord-Trøndelag Health Study)	N = 21892, 42.7% males	11 years Baseline: 1984-1986 Follow-up: 1995-1997	Self-reported leisure time PA Total score – Low – Medium – High Frequency (per wk) – None – <1 – 1 – 2-3 – ≥4 Intensity – None – Low – Medium/high	Incident hypertension (measured by study team)	RR [95% CI] Risk of hypertension not associated with PA total score[+4]: Women | Men – Low: 1.0 (reference) – Medium: 0.98 [0.92, 1.05] | 0.96 [0.90, 1.03] – High: 0.96 [0.90, 1.01] | 0.97 [0.90, 1.03] p = 0.138 | p = 0.276 Frequency of PA associated with reduced risk of hypertension only in males (≥4/wk: RR 0.87 [0.78, 0.98]). Obese males with high PA have lower risk of hypertension (RR 1.16 [0.79, 1.70]) than obese males with low PA (RR 1.50 [1,27, 1.77]). Obese females with low PA have increased risk of hypertension (RR 1.55 [1.35, 1.77]).
Williams & Thompson (2012)	USA	N = 43893	Median 6.2 years Baseline: 1998-1999 Follow-up: 2006	Self-reported PA METh/d – Light – Moderate – Vigorous	Incident hypertension	Greater METh/d is associated with lower risk of incident hypertension HR [95% CI][+5] – Running: 0.958 [0.94, 0.97] – Walking: 0.928 [0.899, 0.957] – Other vigorous: 0.98 [0.97, 0.99] – Other moderate: 0.997 [0.976, 1.018] – Other light: 0.886 [0.739, 1.006]

Abbreviation: CI – confidence interval, d – day, h – hour, HR – hazard ration, IQR – interquartile range, MET – metabolic equivalent, min – minutes, MPA – moderate physical activity, MVPA – moderate to vigorous physical activity, N – number of participants, N.A. – not available, p – p-value, PA – physical activity, RR – relative risk, SE – standard error, wk – week

[+1]: Model adjusted for age, gender and follow-up time; [+2] Model adjusted for sex*time, age, education levels, marital status, current smoking, alcohol intake*time, total energy intake, sleeping hours, leisure/ working METs/min/wk; [+3] Model adjusted for sociodemographic (age, education, marital status, area of residence), behavioral (smoking, alcohol, and sitting), chronic conditions covariates; [+4] Model adjusted for age, marital status, education, smoking, alcohol frequency last 2 weeks, BMI, PA summary score; [+5] Model adjusted for baseline age (age, age2), sex, race, education, smoking, intakes of red meat, fruit, alcohol, preexisting CHD at baseline

2.5 Discussion

The purpose of this research was to review studies published after January of 2012 and up to February of 2019 that investigated the long-term association between PA and new onset of obesity, CHD, diabetes and hypertension. Overall, we observed an association between PA and a decreased risk of incident obesity, CHD and diabetes but not hypertension. This is in line with systematic reviews published by our group and others that also found beneficial associations of PA with overweight/ obesity, CHD and diabetes (Aune et al., 2015; Chin et al., 2016; Reiner et al., 2013; Sattelmair et al., 2011). Furthermore, it is also consistent with our hypothesis derived from both interventional and observational studies (Rodrigues et al., 2016; Shaw et al., 2006; Tam & Yeung, 2018; Wilks et al., 2011).

The included studies that examined the association between PA and incident hypertension reported conflicting results. This is partly in accordance with two other meta-analyses (Huai et al., 2013; Liu et al., 2017). One meta-analysis reported a reduction of incident hypertension by 6 % for each 10 metabolic equivalent of task hours per week increment of leisure time PA (Liu et al., 2017). However, another meta-analysis detected an inverse association for recreational PA and incident hypertension but not for occupational PA (Huai et al., 2013). Of note, the causes of hypertension are multifactorial and the way they interact and ultimately contribute to the development of hypertension is unclear. Thus, potential mechanisms for prevention of hypertension through PA also remain unclear.

Some studies included in this review also reported findings stratified by sex and body weight. For example, one study observed a gradual inverse association between frequency, duration and intensity of PA and risk of incident diabetes in males, but only a gradual inverse association between frequency and intensity of PA and risk of incident diabetes in females (Hjerkind et al., 2017). Additionally, another study reported that, while overall PA irrespective of body weight was not associated with the outcome of incident hypertension, obese males with high PA had a significantly lower risk of hypertension than obese males with low PA (Stenehjem et al., 2018).

The quality of included studies was independently assessed by two reviewers and was rated as moderate to good, with scores ranging between 16 and 22 (total range: 0-22). This is not surprising since we only included studies published in or after 2012 that may already have followed quality guidelines on reporting findings of observational studies such as STROBE (Elm et al., 2007). The potential risk of bias was rated moderate to poor and there were several concerns that warrant brief discussion: 1) All studies included in this review assessed PA through self-reported questionnaires which may be prone to recall bias. However, given the large sample sizes and since the baseline measurements of PA of many studies took place several years or even decades ago, objective measurement of PA might not have been feasible. There is good reason to believe that more longitudinal studies using novel objective techniques such as accelerometry (e.g. LaCroix et al., 2019; Lee et al., 2018) will become available in the near future. 2) The studies differed regarding the assessment of the outcomes of interest, e.g. some studies objectively measured blood glucose levels or blood pressure (e.g. Medina et al., 2018; Stenehjem et al., 2018) whereas others relied on self-reported information by the study participants and/ or medical chart review (e.g. Cohen et al., 2012; Elwood et al., 2013). 3) The studies differed in terms of adjustment for potential confounders and mediators which makes a comparison of findings between studies difficult. 4) Five studies were conducted only among males (Elwood et al., 2013; Ferrario et al., 2018; Jefferis et al., 2012; Jefferis et al., 2014; Shi et al., 2013) and five studies were conducted only among females (Chomistek et al., 2016; Cohen et al., 2012; Grøntved et al., 2014; Mehlig et al., 2014; Pavey et al., 2013).

We did not investigate potential mechanisms underlying the associations between PA and incident obesity, diabetes and CHD. However, it has previously been postulated that there are acute and chronic effects of PA on insulin resistance, which may account for improvements in insulin action and decreased blood glucose levels as a response to engagement in PA (Colberg et al., 2010). Additionally, PA impacts energy balance by increasing total energy expenditure, which in turn causes an energy deficit and may lead to lower body weight (Jakicic et al., 2018). Stimulating responses in adipose and body tissues by PA may also influence total energy balance and body composition (Jakicic et al., 2018). Furthermore, studies suggest that regular PA increases capillarization and may reverse endothelial alterations, which is a major risk factor for CHD (Winzer et al., 2018).

The strengths of this review are the rigorous search and selection strategy following published guidelines and conducted by two reviewers. Also, both quality and potential risk of bias were assessed by two authors independently. We deliberately focused on studies published after January of 2012 in order to provide an update of a systematic review previously published by our group (Reiner et al., 2013). In addition, even though unintentional, our review included studies from various countries such as Sweden, Norway, UK, Greece, Mexico, China, Australia, Italy, US, the Netherlands, Germany, France, Spain and Denmark which may add to the generalizability of our observations. The major limitations of this review pertain to the relatively small number of included studies. This may be due to the fact that we only included studies with large sample size ($N \geq 500$) and relatively long follow-up time of ≥ 5 years. However, we believe that these criteria ensure validity of our conclusions and a higher probability of generalizability of the study findings. In addition, a large body of research on PA and overweight/ obesity published after 2012 focused on change in BMI or body weight over time. We opted to not include these studies in our review as we chose our outcome of interest to be incident obesity, and information on change in BMI or body weight over time is thus not sufficient. For instance, a person could be underweight at baseline and an increase in BMI or weight might actually reflect progression to a healthier body constitution. At the same time, we also acknowledge that particularly obesity and hypertension are conditions for which individuals can take action to improve, i.e., a person develops incident obesity but may be able to decrease body weight in order to progress back to overweight or normal weight. Furthermore, our search terms may have been too narrow or not comprehensive enough and there may be published studies that we were not able to identify. However, in order to compensate for this potential shortcoming, we also manually searched bibliographies of included studies. Finally, the studies differed with regard to the depth of investigating PA variables. As such, PA was only one of many predictors in some studies (e.g. Carlsson et al., 2013; Ekelund et al., 2012) and thus only one finding related to PA and the outcome of interest was reported. Whereas in other studies, the association between various PA parameters (e.g. type, intensity, frequency, duration) and the outcome of interest was examined (e.g. Ferrario et al., 2018; Stenehjem et al., 2018).

More research to untangle the association and potential underlying mechanisms between PA and the outcome of incident overweight, CHD, diabetes and hypertension is needed, preferably using prospective cohort studies with large sample sizes, long follow-up and objective measurement of both predictor variable (i.e. PA) and the outcomes of interest. In addition, metaanalytic approaches to address research questions pertaining the association between PA and various health outcomes are warranted.

2.6 Conclusion

Overall, this systematic review replicates, updates, and extends the growing body of research on the associations between PA and incident obesity, CHD and diabetes. No clear association between PA and reduced risk for hypertension was detected. This review emphasizes the contribution of PA in the prevention of various chronic diseases. Reducing the risk of new onset of NCDs and thereby reducing the economic burden on health systems is of high importance to societies worldwide. Regional and global action plans and preventive strategies (e.g. Mnich, 2019) should highlight the beneficial impact of regular PA and support national governments in the implementation of concrete actions towards achieving a higher engagement in PA among individuals across all ages.

Abbreviations

BMI: Body mass index; CHD: Coronary heart disease; NCDs: Noncommunicable diseases; PA: Physical activity; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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Authors' contributions

LC & JKR conducted the literature search, and extracted and interpreted data. LC wrote the first draft of the manuscript. JKR, CN and AW revised the manuscript. All authors read and approved the final manuscript.

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All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflicts of interest pertaining to this manuscript.

All references of publication I are included in the list of references at the end of this thesis.

3 Longitudinal association between physical activity and the risk of incident metabolic syndrome in middle-aged adults in Germany

Publication II: Longitudinal association between physical activity and the risk of incident metabolic syndrome in middle-aged adults in Germany

Slightly modified version of the published manuscript.

Cleven, L., Krell-Roesch, J., Schmidt, S. C. E., Dziuba, A., Bös, K., Jekauc, D. & Woll, A. (2022). Longitudinal association between physical activity and the risk of incident metabolic syndrome in middle-aged adults in Germany. *Scientific reports, 12*(1). https://doi.org/10.1038/s41598-022-24052-5

3.1 Abstract

We examined the longitudinal association between physical activity (PA) and the risk of incident metabolic syndrome (MetS) among middle-aged, community-dwelling adults, including 591 individuals (314 females; mean (SD) age, 43.8 (8.5) years) who were free of MetS at baseline. Habitual and sports-related PA was assessed by a self-reported questionnaire. MetS was defined based on HDL-cholesterols, triglycerides, glucose or HbA1c, blood pressure, and waist circumference. We calculated Cox proportional hazard ratios (HR) and 95 % confidence intervals (CI) using regression analyses. Over a mean follow-up of 12.5 years, 205 participants developed incident MetS. Four different sports-related PA measures were associated with a decreased risk of incident MetS: (1) Engaging in ≥ 75 min/ week (HR 0.71, 95 % CI 0.53-0.94), (2) maintaining a continuously high amount from baseline to follow-up of ≥ 75 min/ week (HR 0.66, 95 % CI 0.46-0.94), (3) starting from < 150 min/ week at baseline to ≥ 150 min/ week at follow-up (HR 0.65, 95 % CI 0.45-0.94), and (4) increasing from < 16.6 MET-hours/ week at baseline to ≥ 16.6 MET-hours/ week at follow-up (HR 0.47, 95 % CI 0.31-0.71). Thus, maintaining, starting or increasing sports-related PA is associated with a lower risk of incident MetS.

3.2 BACKGROUND

Metabolic syndrome (MetS) refers to a cluster of cardiometabolic risk factors, including abdominal obesity, elevated blood glucose, elevated blood pressure, or dyslipidemia (elevated triglycerides and lowered high-density lipoprotein cholesterol; HDL) (Alberti et al., 2009), and is considered a non-communicable disease (NCD). NCDs have a major impact on economies and societies worldwide and have been identified as the leading reason for 73 % of all global deaths, with 28.8 million deaths attributed to risk factors such as high blood pressure, high blood glucose, or high body mass index (BMI) (Foreman et al., 2018; The Lancet, 2018; World Health Organization, 2018). The prevalence of MetS has increased over the past decades (Saklayen, 2018). Therefore, it is critical to identify potential preventive factors and mechanisms for MetS.

In adults, decreased metabolic risk factors such as hypertension, overweight and obesity, or hyperglycemia, as well as favorable health-related behaviors such as limited tobacco or alcohol consumption, plant-based diet, and physical activity (PA) may be effective in preventing new onset of MetS. A growing body of research has reported a positive effect of PA on cardiometabolic risk factors, e.g., being physically active may reduce body weight and blood pressure, elevate high-density lipoprotein-cholesterols, lower triglycerides, and improve insulin resistance (Franklin, 2008; Myers, 2014; Myers et al., 2019; Pucci et al., 2017; Sallis et al., 2016).

The World Health Organization (WHO) recommends at least 150 minutes of moderate to vigorous PA, or 75 minutes of vigorous-intensity PA per week to achieve health benefits (World Health Organization, 2020), which is equivalent to at least 8.3-16.6 metabolic equivalent-hours (METh) per week (= 500-1000 MET-minutes per week) (U.S. Department of Health and Human Services, 2018). However, it remains unknown as to how much PA is needed to reduce the onset of MetS, or whether changes in PA behavior are related to the risk of incident MetS.

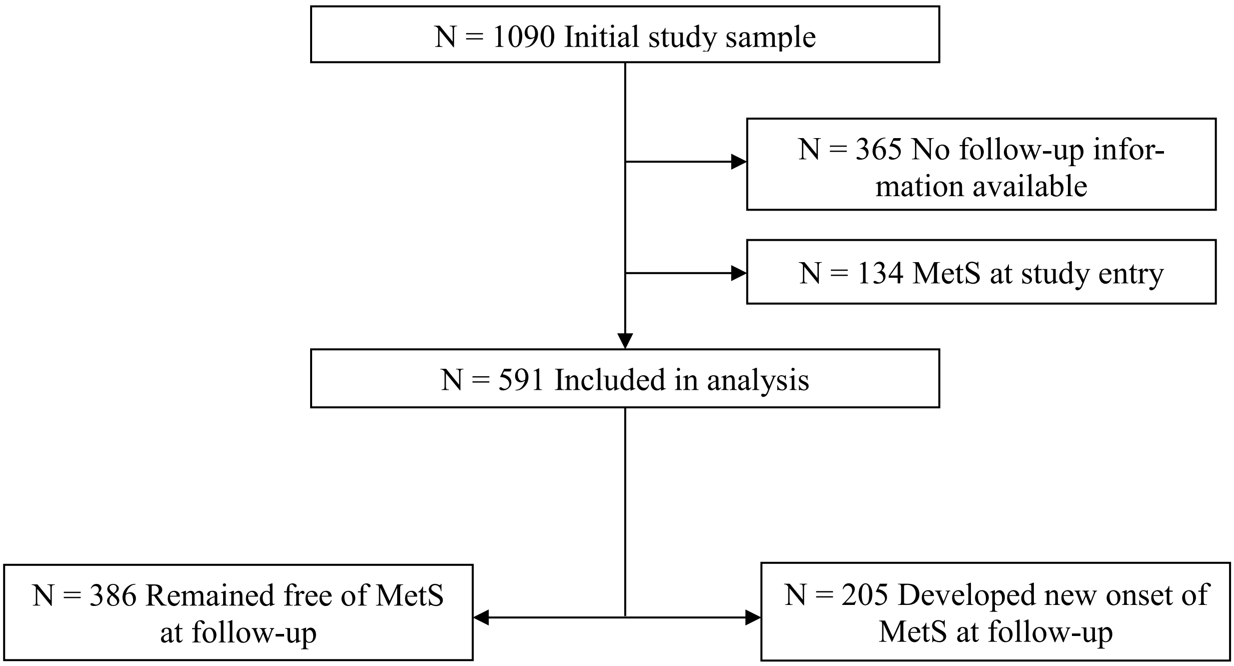
The aim of this study was thus to examine the longitudinal associations between various PA variables (i.e., habitual PA level, sport-related PA level (minutes and METh), and change in PA behavior over time) and the risk of incident MetS among middle-aged males and females in a community-based sample from South-Western Germany over a period of 29 years.

3.3 METHODS

3.3.1 STUDY DESIGN AND POPULATION

'Gesundheit zum Mitmachen' is an ongoing, community-based longitudinal cohort study of middle-aged and older adults living in the city of Bad Schönborn in South-Western Germany with six measurement points (1992, 1997, 2002, 2010, 2015, 2021). Detailed information about the design and methods of the study has been described elsewhere (Tittlbach et al., 2017; Woll et al., 2004). The study was approved by the ethics committee of the Karlsruhe Institute of Technology (KIT), Germany and was conducted in accordance with the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations.

Briefly, individuals residing in Bad Schönborn, Germany were randomly selected from the local residents' registration offices and were invited to participate in the study. Participants who took part in the study at least once were re-invited for every measurement point, and new samples of participants aged 33-37 years were included at each measurement time point to prevent sample attrition. Participation in the study was voluntary and all participants provided written informed consent. At each of the six measurements points, participants provided information about self-rated health status, habitual and sports-related PA, and sociodemographic information through a self-reported questionnaire, underwent an objective health status examination conducted by a licensed physician, and had a fasting blood sample drawn.



Abbreviation: N = number of participants

FIGURE 8: FLOW CHART OF STUDY PARTICIPATION (CHAPTER 3)

For the current analysis, from a total of 1090 individuals who participated in this study, we excluded participants with pre-existing MetS (i.e., outcome of interest) at baseline (N = 134) and individuals with no longitudinal data information available (N = 365). A total of 591 participants were thus included in the final analysis (please refer to Figure 8 for a flow chart).

3.3.2 Physical activity assessment (predictor variables)

Habitual PA. We calculated an index to quantify the amount of habitual PA at baseline (minutes per week) as indicator for recreational PA level (thus deliberately excluding sports activity participation) by creating a sum index that was derived from participants‘ self-reported information about daily minutes of walking, biking for transportation, as well as working in the household and gardening. For statistical analysis, the sample was divided into two groups (i.e., inactive: < 75 minutes/ week, and active: ≥ 75 minutes/ week) as well as three groups (i.e., low: < 75 minutes/ week, medium: 75-149 minutes/ week, and high: ≥ 150 minutes/ week) based on the calculated index.

Sports-related PA. An index for the volume of sports-related PA at baseline was calculated from information provided by participants about frequency (i.e., number of weekly exercise sessions), duration (i.e., minutes per session), intensity (i.e., not very intense, moderately intense with some sweating, and highly intense with much sweating), and type of weekly sports-related PA (Oja et al., 1994). For statistical analyses, the sample was divided into two groups (i.e., inactive: < 75 minutes/ week, active: ≥ 75 minutes/ week) based on the index. In a next step, we also created three groups based on the global recommendation on PA level (i.e., low: < 75 minutes/ week, medium: 75-149 minutes/ week, high: ≥ 150 minutes/ week) (World Health Organization, 2010). Furthermore, to consider the intensity level of the activity, every type of sport was assigned a specific MET-value (Ainsworth et al., 2011), and by multiplication with the time spent carrying out the respective activity, sports-related PA level in MET-hours (METh) per week at baseline was calculated. For statistical analysis, in the sample was divided into two groups (i.e., not active: < 8.3 METh/ week, active: ≥ 8.3 METh/ week), as well as three groups (not active: < 8.3 METh/ week, moderately active: 8.3-16.5 METh/ week, highly active: ≥ 16.6 METh/ week) based on the sports-related PA level.

Change of sports-related PA categories (volume: minutes and METh). To assess the change in minutes of sports-related PA (per week), differences in PA level between baseline and the latest follow-up examination were calculated individually for each participant. Four categories by applying two different thresholds, i.e., 75 and 150 minutes per week, respectively, based on WHO guidelines on physical activity and sedentary behavior (World Health Organization,

2020) were calculated. The four categories were *Stable inactive* (i.e., individuals who continuously reported less than 75/ 150 minutes/ week sports-related PA); *Quits activity* (i.e., participants who reported more than 75/ 150 minutes/ week sports-related PA at baseline but not follow-up); *Starts activity* (i.e., individuals who reported less than 75/ 150 minutes/ week sports-related PA at baseline but more than 75/ 150 minutes/ week at follow-up); and *Stable active* (i.e., participants who reported continuously more than 75/ 150 minutes/ week of sports-related PA). Similarly, to assess the change in METh of sports-related PA, differences in METh level at baseline examination compared to the latest follow-up examination were calculated. Then four groups were created: *Stable low* (i.e., individuals who continuously reported less than 16.6 METh/ week sports-related PA), *Decreasing* (i.e., participants who reported more than 16.6 METh/ week sports-related PA at baseline but not at follow-up); *Increasing* (i.e., individuals who reported less than 16.6 METh/ week sports-related PA at baseline but more than 16.6 METh/ week at follow-up); and *Stable high* (i.e., participants who reported continuously more than 16.6 METh/ week sports-related PA).

All information regarding habitual and sports-related PA at baseline examination and follow-up was assessed by a self-reported questionnaire (test-retest reliability after two weeks: $r > .90$, $\alpha = .94$) (Jekauc, 2009).

3.3.3 Metabolic syndrome assessment (Outcome of interest)

At baseline and each follow-up examination, the status of MetS was assessed by self-reported medication and/ or through examination by a licensed physician.

Metabolic syndrome. According to the Joint Interim Statement harmonized criteria, we defined having or developing new onset of MetS, when at least three out of five risk factors (i.e., elevated blood glucose, elevated blood pressure, lowered HDL, elevated triglycerides, or abdominal obesity) were present at baseline examination or at follow-up (Alberti et al., 2009).

Elevated blood glucose. Elevated blood glucose was determined by a physician at baseline and each follow-up examination based on blood-glucose levels (i.e., for measurement points 1992 to 2015: fasting blood-glucose level ≥ 100mg/dL (Alberti et al., 2009) or non-fasting blood-glucose level ≥ 200mg/dL (Roden, 2016); and for measurement in 2021: HbA1c ≥ 6,5 % (Roden, 2016)). Furthermore, a participant was classified as having elevated blood glucose, if a diabetes diagnosis had been made previously by a physician or if the participant was on diabetes medication, i.e., participants were asked: Do you take any medication to lower blood-glucose levels?

Elevated blood pressure. Blood pressure was assessed at baseline and each follow-up examination by standardized measurement. A participant was classified as having elevated blood pressure if the systolic value was greater than 130 mmHg or if the diastolic value was greater than 85 mmHg in the measurement. Furthermore, a participant was classified as having elevated blood pressure if hypertension diagnosis had been made previously by a physician, or if the participant was on blood pressure medication (Alberti et al., 2009), i.e., participants were asked: Do you take any medication to lower your blood pressure?

Blood Lipids (triglycerides and high-density lipoprotein-cholesterol). Blood lipids were assessed at baseline and at each follow-up examination by standardized measurement. Participants were classified as having high triglycerides when the levels were greater than 150 mg/dL, and as having low HDL-cholesterol when the levels were lower than 40mg/dL for males and lower than 50mg/dL for females, respectively (Alberti et al., 2009). Furthermore, a participant was classified as having critical level of blood lipids (i.e., high triglycerides or low HDL-cholesterol) if the diagnosis had been made previously by a physician or if the participant was on medication for the respective condition, i.e., participants were asked: Do you take any medication to lower blood lipids?

Abdominal Obesity. Waist circumference (in cm) was assessed at baseline and at each follow-up examination by standardized measurement. A participant was classified as having abdominal obesity when the waist circumference was greater than 102 cm for males and greater than 88 cm for females, respectively (National Institutes of Health, 1998; World Health Organization, 2000).

Assessment of confounders. Traditional demographic variables (e.g., age and sex) were assessed though self-reported questionnaire. We also determined socio-economic status (SES) based on information provided by participants about formal education and professional status of themselves or their significant others (usually the spouse), if participants were not working. Four SES categories were used for statistical analysis, i.e., low, low/ medium, medium/ high and high SES (Hradil, 1987; Woll et al., 2004).

3.3.4 Statistical analysis

Selected sociodemographic, behavioral, and health-related characteristics of the participants were used to characterize the cohort at baseline by using means (M) and standard deviation (SD). Cox proportional hazards regression models were calculated to examine the associations between various PA predictor variables (i.e., volume of habitual and sports-related PA at baseline, and change in volume of sports-related PA level from baseline to follow-up; variables were nominal coded or dummy coded), and the risk of incident MetS. For the analysis, only participants who were free of MetS at baseline and had at least one follow-up measurement were included. Date of entry in the study was used as baseline and was determined individually for each participant. Follow-up time (in months) was calculated individually for each participant from baseline until the first event (i.e., incident MetS) occurred or loss to follow-up, whichever happened first. Missing values were treated as missing at random, which yielded in a pairwise deletion of cases with at least one missing value among either predictor or outcome variable for each analysis. Numbers of missing values are provided in the result table for each category of PA, respectively. We calculated Hazard Ratios (HRs) and 95 % confidence intervals (CI) based on regression analyses for each category of PA as compared to the least active group which was always set as reference group. For each predictor, we ran two sets of models: unadjusted models (Model 1), and models adjusted for traditional confounding variables, i.e., age, sex and SES (Model 2). Analyses were performed using SPSS software version 27, and using the conventional alpha level of 0.05 to determine statistical significance. A HR > 1.0 was considered as indicating an elevated risk for incidence of MetS, a HR < 1.0 was considered as indicating a reduced risk for incidence of MetS.

3.4 RESULTS

3.4.1 SAMPLE CHARACTERISTICS

Baseline demographics of study participants are shown in Table 6. Data of participants who were free of MetS at baseline and with follow-up information were available on 591 individuals. Mean age at baseline was 43.8 (SD 8.5) years, and 53.1 % of participants were female. Habitual PA was performed for a mean of 341.37 (SD 266.05) min/ week. Sports-related PA was performed for a mean of 101.84 (SD 133.58) min/ week, and with a mean of 12.04 (SD 15.96) METh/ week, and it was most frequently performed for less than 75 minutes/ week (53.4 %). Please refer to Table 7 for an overview of frequencies with regard to PA change variables from study entry to the latest follow-up examination.

Of all participants included in the analysis, 266 (45.0 %) had one follow-up assessment, 128 (21.7 %) participants had two follow-up assessments, 97 (16.4 %) participants had three follow-up assessments, 61 (5.6 %) had four follow-up assessments, and 39 (3.6 %) participants had 5 follow-up assessments. The mean (SD) time of follow-up assessments was of 2.1 (1.3). After a mean follow-up time of 12.5 (SD 8.3, range 5-29) years, 205 (34.7 %) participants developed incident MetS and 386 (65.3 %) remained free of MetS at follow-up (please refer to Figure 8) with 7373 person-years (sum of the time spans for each participant under observation). The risk of incident MetS did not statistically significantly differ between males (51.2 %) and females (48.8 %). The mean age at which MetS was first diagnosed was 56.8 (SD 9.5; range: 38-81) years. Cases of incident MetS were more frequent in older than younger persons (75.1 % cases of MetS occurred in participants aged > 50 years).

TABLE 6: PARTICIPANT DEMOGRAPHICS AT BASELINE

	Total	**Males**	**Females**
N	591	277	314
Sex (%)	-	46.9	53.1
Age [years], mean (SD)	43.81 (8.53)	43.91 (8.61)	43.71 (8.46)
SES (%)			
Low	13.2	12.0	14.2
Low/medium	20.2	19.7	20.7
Medium/high	43.4	40.1	46.3
High	23.2	28.1	18.8
Elevated waist circumference, %	15.8	14.2	17.5
Elevated triglycerides, %	7.6	11.9	3.8
Reduced HDL, %	12.4	10.8	13.7
Elevated blood pressure, %	50.8	62.1	40.8
Elevated blood glucose, %	1.5	2.5	0.6
BMI [kg/m^2], mean (SD)	24.97 (3.41)	25.89 (2.96)	24.15 (3.57)
Normal (< 25) (%)	56.6	43.8	6.8
Overweight (25-29) (%)	35.4	47.5	24.8
Obese (≥ 30) (%)	8.0	8.7	7.3
Habitual PA [min/week], mean (SD)	341.37 (266.05)	368.80 (295.94)	317.27 (234.53)
Low (< 75) (%)	5.2	5.1	5.4
Medium (75-149) (%)	24.0	23.5	24.5
High (≥ 150) (%)	70.7	71.5	70.1
Sports-related PA [min/week], mean (SD)	101.84 (133.58)	106.95 (143.57)	97.31 (124.14)
Inactive (< 75) (%)	53.4	51.3	55.3
Medium (75-149) (%)	23.1	25.6	20.8
High (≥ 150) (%)	23.6	23.1	24.0
Sports-related PA [METh/week], mean (SD)	12.04 (15.96)	12.83 (17.10)	11.35 (14.87)
Low (< 8.3) (%)	54.0	50.2	57.3
Medium (8.3-16.5) (%)	21.2	24.9	17.8
High (≥ 16.6) (%)	24.9	24.9	24.8
Follow-up time [years], mean (SD)	12.47 (8.30)	12.95 (8.48)	12.05 (8.13)

Abbreviations: BMI = body mass index, kg = kilograms, m= meters, METh = metabolic equivalent hours, min= minutes, N= number of participants, PA= physical activity, SD = standard deviation, SES = socio-economic status. Elevated waist circumference: ≥ 102 cm for males, ≥ 88 cm for females; elevated triglycerides: ≥ 150 mg/dL and/or specific medication; reduced HDL-cholesterols: < 40 mg/dL for males, < 50 mg/dL for females and/or specific medication; elevated blood pressure: systolic value ≥ 130 mmHg or diastolic value ≥ 85 mmHg and/or specific medication; elevated blood glucose: fasting blood-glucose level ≥ 100 mg/dL or non-fasting blood-glucose level ≥ 200 mg/dL or HbA1c ≥ 6,5 % and/or specific medication

Participants across all SES developed incident MetS, with most incident MetS cases (N= 73, 35.6 %) in the medium to high SES group. 134 participants with a mean age of 49.7 (SD 10.6; range: 33-77) years were not included in this analysis as they had prevalent MetS at study entry.

TABLE 7: FREQUENCIES WITH REGARD TO PA CHANGE VARIABLES FROM STUDY ENTRY TO THE LATEST FOLLOW-UP EXAMINATION

	Total	**Males**	**Females**
Change in sports-related PA category over time [min/week], N (%) (missing N=13)			
Stable inactive (< 75 to < 75)	178 (30.8)	79 (29.3)	99 (32.1)
Quits activity (≥ 75 to < 75)	63 (10.9)	34 (12.6)	29 (9.4)
Starts activity (< 75 to ≥ 75)	131 (22.7)	60 (22.2)	71 (23.1)
Stable active (≥ 75 to ≥ 75)	206 (35.6)	97 (35.9)	109 (35.4)
Change in sports-related PA over time [min/week], N (%) (missing N=13)			
Stable inactive (< 150 to < 150)	308 (53.3)	148 (54.8)	160 (51.9)
Quits activity (≥ 150 to < 150)	50 (8.7)	24 (8.9)	26 (8.4)
Starts activity (< 150 to ≥ 150)	134 (23.2)	61 (22.6)	73 (23.7)
Stable active (≥ 150 to ≥ 150)	86 (14.9)	37 (13.7)	49 (15.9)
Change in sports-related PA category over time [METh/week], N (%) (missing N=6)			
Stable low (< 16.6 to < 16.6)	326 (55.7)	154 (56.4)	172 (55.1)
Decreasing (≥ 16.6 to < 16.6)	58 (9.9)	24 (8.8)	34 (10.9)
Increasing (< 16.6 to ≥ 16.6)	114 (19.5)	52 (19.0)	62 (19.9)
Stable high (≥ 16.6 to ≥ 16.6)	87 (14.9)	43 (15.8)	44 (14.1)

Abbreviations: METh = metabolic equivalent hours, min= minutes, N= number of participants, PA= physical activity

3.4.2 ASSOCIATION BETWEEN PHYSICAL ACTIVITY (HABITUAL AND SPORTS-RELATED) AT BASELINE AND INCIDENT METABOLIC SYNDROME

After adjusting for age, sex and SES, engaging in more than 75 minutes of sports-related PA per week at baseline was associated with a 29 % reduced risk of incident MetS (HR 0.71, 95 % CI 0.53-0.94, p= 0.02), compared to participants who reported engaging in less than 75 minutes of sports-related PA per week (please refer to Table 8). Whereas, participating in sports-related PA between 75-149 minutes/ week at baseline was associated with a 38 % decreased risk of incident MetS (HR 0.62, 95 % CI 0.43-0.91, p= 0.01) compared to sports-related PA carried out for less than 75 minutes/ week. For high sports-related PA level (≥ 150 minutes/ week), there was a trend for a reduced risk of incident MetS (HR 0.80, 95 % CI 0.56-1.13, p = 0.20), albeit not statistically significant.

TABLE 8: ASSOCIATION BETWEEN PA VARIABLES AND THE RISK OF INCIDENT METS

No. with incident metabolic syndrome (N=205, 34.7 %)						
	No. at risk (N=591)	**No. incident MetS (% of No. at risk)**	**Model 1 unadjusted Hazard Ratio (95% CI)**	**p-value**	**Model 2 adjusted Hazard Ratio (95% CI)**	**p-value**
Amount of habitual PA level at baseline [min/week]						
Inactive (< 75)	31	11 (1.9)	ref		ref	
Active (≥ 75)	560	194 (32.8)	1.05 (0.57-1.92)	0.88	1.15 (0.61-2.18)	0.66
Amount of habitual PA level at baseline [min/week]						
Low (< 75)	31	11 (1.9)	ref		ref	
Medium (75-149)	142	40 (6.8)	0.80 (0.41-1.57)	0.52	1.00 (0.50-2.01)	0.99
High (≥ 150)	418	154 (26.1)	1.14 (0.62-2.10)	0.68	1.20 (0.63-2.27)	0.58
Volume of sports-related PA level at baseline [min/week] (missing N=1)						
Inactive (< 75)	315	126 (21.3)	ref		ref	
Active (≥ 75)	275	79 (13.4)	**0.62 (0.47-0.83)**	**<0.01**	**0.71 (0.53-0.94)**	**0.02**
Volume of sports-related PA level at baseline [min/week] (missing N=1)						
Low (< 75)	315	126 (21.3)	ref		ref	
Medium (75-149)	136	36 (6.1)	**0.53 (0.37-0.77)**	**<0.01**	**0.62 (0.43-0.91)**	**0.01**
High (≥ 150)	139	43 (7.3)	0.73 (0.52-1.04)	0.08	0.80 (0.56-1.13)	0.20
Change in sports-related PA category over time [min/week] (missing N=13)						
Stable inactive (< 75 to < 75)	178	73 (12.4)	ref		ref	
Quits activity (≥ 75 to < 75)	63	18 (3.0)	**0.59 (0.35-0.99)**	**0.05**	0.71 (0.42-1.20)	0.20
Starts activity (< 75 to ≥ 75)	131	51 (8.6)	0.75 (0.52-1.07)	0.12	0.84 (0.59-1.21)	0.35
Stable active (≥ 75 to ≥ 75)	206	61 (10.3)	**0.55 (0.39-0.76)**	**<0.01**	**0.66 (0.46-0.94)**	**0.02**
Change in sports-related PA category over time [min/week] (missing N=13)						
Stable inactive (< 150 to < 150)	308	119 (20.1)	ref		ref	
Quits activity (≥ 150 to < 150)	50	18 (3.0)	0.88 (0.54-1.44)	0.61	0.94 (0.57-1.54)	0.79
Starts activity (< 150 to ≥ 150)	134	40 (6.8)	**0.56 (0.39-0.80)**	**<0.01**	**0.65 (0.45-0.94)**	**0.02**
Stable active (≥ 150 to ≥ 150)	86	26 (4.4)	0.70 (0.46-1.07)	0.10	0.77 (0.50-1.18)	0.23

	No. at risk (N=591)	No. incident MetS (% of No. at risk)	Model 1 unadjusted Hazard Ratio (95% CI)	p-value	Model 2 adjusted Hazard Ratio (95% CI)	p-value
Volume of sports-related PA at baseline [METh/week]						
not active (< 8.3)	319	123 (20.8)	ref		ref	
active (≥ 8.3)	272	82 (13.9)	**0.74 (0.56-0.98)**	**0.04**	0.80 (0.60-1.06)	0.13
Volume of sports-related PA at baseline [METh/week]						
not active (< 8.3)	319	123 (20.8)	ref		ref	
moderately active (8.3-16.5)	125	36 (6.1)	**0.67 (0.46-0.98)**	**0.04**	0.75 (0.52-1.10)	0.14
highly active (≥ 16.6)	147	46 (7.8)	0.81 (0.57-1.13)	0.21	0.84 (0.60-1.18)	0.32
Change in sports-related PA category over time [METh/week] (missing N=6)						
Stable low (< 16.6 to < 16.6)	326	131 (22.2)	ref		ref	
Decreasing (≥ 16.6 to < 16.6)	58	19 (3.2)	0.79 (0.49-1.29)	0.35	0.82 (0.51-1.33)	0.43
Increasing (< 16.6 to ≥ 16.6)	114	27 (5.6)	**0.43 (0.28-0.64)**	**<0.01**	**0.47 (0.31-0.71)**	**<0.01**
Stable high (≥ 16.6 to ≥ 16.6)	87	27 (5.6)	0.70 (0.46-1.06)	0.09	0.73 (0.48-1.11)	0.14

Abbreviations: CI = confidence interval, METh = metabolic equivalent hours, min = minutes, N= number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status. Model 1: unadjusted; Model 2: adjusted for age, sex und SES. Significant values are in [bold]

With regard to METh of sports-related PA, being physically active with more than 8.3 METh/ week at baseline was associated with a reduced risk of incident MetS (HR 0.74, 95 % CI 0.56-0.98, p= 0.04) only in the unadjusted model, and the association was no longer statistically significant after adjusting for confounding variables (Model 2: HR 0.80, 95 % CI 0.60-1.06, p= 0.13).

Habitual PA was not statistically significantly associated with the risk of incident MetS in our dataset.

3.4.3 Association between change of sports-related physical activity (minutes and METh) categories over time and incident metabolic syndrome

After adjusting for age, sex and SES, being stable active (stable ≥ 75 minutes/ week from baseline to follow-up) was associated with a 34 % reduced risk of incident MetS (HR 0.66, 95 % CI 0.46-0.94, p= 0.02) compared to being stable inactive (please refer to Table 8). Similarly, for participants who were stable active (stable ≥ 150 minutes/ week from baseline to follow-up), a trend for a reduced risk of incident MetS was observed (HR 0.77, 95 % CI 0.50-1.18, p= 0.23), albeit not statistically significant. Furthermore, participants who reported starting to engage in sports-related PA from < 150 minutes/ week at baseline to ≥ 150 minutes/ week at follow-up, had a 35 % reduced risk of incident MetS (HR 0.65, 95 % CI 0.45-0.94, p= 0.02) as compared to participants who continuously remained inactive. In addition, increasing sports-related PA from < 16.6 METh per week at baseline to ≥ 16.6 METh per week at follow-up, was associated with a 53 % reduced risk of incident MetS (HR 0.47, 95 % CI 0.31-0.71, p< 0.01) compared to participants with a stable low sports-related PA. For participants who reported a stable high sports-related PA (stable ≥ 16.6 METh/ week), a trend for a reduced risk of incident MetS was observed (HR 0.73, 95 % CI 0.48-1.11, p= 0.14), albeit not statistically significant.

3.5 Discussion

Our study adds to the current body of evidence on an association between higher PA at baseline and a decreased risk of incident MetS in middle-aged adults, with risk reductions ranging from 29 % to 38 % for sports-related but not habitual PA. In addition, even though the association between the volume of sports-related PA carried out for ≥ 150 min per week and incident MetS was not statistically significant, the point estimate was below 1.0 indicating a trend for a reduced risk of incident MetS. The WHO currently recommends engaging in at least 75 to 150 min per week of PA for adults. Based on our data, even a threshold of engaging in sports-related PA for at least 75 min per week may be associated with a reduced risk of incident MetS. Researchers and stakeholders may thus want to consider this threshold in the design and conduct of PA programs or public health strategies aimed at promoting metabolic health in the general population.

In addition, favorable changes in sports-related PA from baseline to follow-up were associated with reduced risks of incident MetS. Our results show that engaging continuously in sports-related PA for ≥ 75 min/ week from baseline to follow-up was associated with a 34 % reduced risk of incident MetS as compared to being permanently inactive from baseline to follow-up. The point estimates for the association between engaging continuously in ≥ 150 min/ week of sports-related PA and incident MetS were below 1.0 which is indicative of a reduced risk for new onset of MetS, albeit not statistically significant. Thus, these findings underline the importance of maintaining continuous engagement in sports-related PA across the lifespan in order to achieve desirable health benefits with regard to MetS risk reduction. Nevertheless, our results also show that starting engaging in sports-related PA from < 150 to ≥ 150 min/ week was associated with a 35 % reduced risk of incident MetS compared to participants who continuously remained physically inactive. This indicates that it may never be too late to start engaging in sports-related PA, albeit higher volumes seem to be necessary when starting at older age and/ or later date.

Furthermore, aside from the volume of sports participation in minutes per week as described above, METh also appear to be important. For example, we observed that increasing PA intensity level from < 16.6 METh/ week at baseline to ≥ 16.6 METh/ week at follow-up was statistically significantly associated with a 53 % reduced risk of incident MetS.

Overall, our results are in line with previous longitudinal studies. For example, the Tromsø Study with a total sample of 17,014 individuals, reported a significant inverse association between leisure-time PA at baseline and incident MetS, with a more than 40 % reduced risk of incident MetS over a mean follow-up of 13.8 years (with a maximum of 22 years) (Wilsgaard & Jacobsen, 2007). Whereas, investigators from the Atherosclerosis Risk in Communities study reported only a weak association between PA and incident MetS in a sample of 9,359 males and females and based on a follow up time of 6 years (Cheriyath et al., 2010). Furthermore, two meta-analyses showed that high as compared to low PA levels were associated with a reduced risk of MetS, and risk reductions ranged from 10-20 % (He et al., 2014; D. Zhang et al., 2017). Conflicting results have been reported in the literature with regard to associations between PA METh at baseline and risk of incident MetS, and the association may also be sex-specific. For example, a trend for a decreased risk of MetS with increasing dose of PA was reported in men, whereas a decreased risk in women was observed only for high or very high levels of baseline

PA in a sub-cohort of the Japan Epidemiology Collaboration on Occupational Health Study with a total of 22,383 participants included and a mean follow-up time of 4.1 years (maximum 5 years) (Kuwahara et al., 2016). Furthermore, the Copenhagen City Heart Study including 3,968 men and women, revealed that moderate and high but not light PA volumes were associated with a lower risk of MetS, with about 50 % risk reduction over a follow-up time of 10 years (Laursen et al., 2012). With regard to the association between changes in PA levels from study entry to follow-up and incident MetS, results of a longitudinal study conducted in Brazil showed a 65 % reduced risk to develop MetS for permanently active participants compared to permanently inactive participants, whereas starting PA reduced the risk of incident MetS about 45 % (Werneck et al., 2020). Similarly, the Coronary Artery Risk Development in Young Adults study, including 4,192 men and women, reported that maintaining regular PA over time was associated with a 35 % reduced risk of MetS during a mean follow-up time of 13.6 years (with a maximum up to 15 years) (Carnethon et al., 2004).

A major strength of our study is the longitudinal design with a long follow-up period of 29 years. To the best of our knowledge, only a few studies exist with such a long follow-up time (e.g., Harvard Alumni Study (Paffenbarger et al., 1978), Framingham Heart Study (Dawber et al., 1951), National Health and Nutritional Examination Survey (Barkley, 2008), Nurses' Health Study (Belanger et al., 1978)). In addition to previous studies, our analysis focused not only on the volume of sports-related PA at baseline, but also considered habitual activity and change in sports-related PA during follow-up. Furthermore, self-reported health status of participants was augmented by a health examination performed by a licensed physician.

Limitations of our study pertain to the rather small sample with participants predominantly having medium to high SES. Thus, our results may not be transferable to communities of middle-aged adults with lower SES. In addition, PA was assessed by a self-reported questionnaire which may be prone to recall bias, i.e., PA may have been over- or underestimated by participants. However, the questionnaire used in our study has been tested for reliability (test-reliability for two weeks $r > .90$) and internal consistency ($\alpha = .94$) (Jekauc, 2009). Furthermore, we did not examine changes in PA between childhood or youth and adulthood, or between early and middle adulthood. It is known that participation in PA varies across the lifespan, e.g., sports behavior is rather stable from childhood to youth (Telama et al., 2005), whereas PA behavior in adulthood is instable (Gordon-Larsen et al., 2004). Even though our study is in line with previous studies among adults that also provided evidence of an association between higher PA levels at baseline and favorable health outcomes at later life (e.g. Cleven et al., 2020), future research may want to focus more closely on PA behavior changes across the lifespan.

In our study, we considered new onset of MetS as the outcome of interest. However, due to its definition, the status of MetS may fluctuate over time in participants, particularly as we had several measurement points. However, the majority of participants had only one (45 % of participants) or two follow-up examinations (21.7 % of participants). Furthermore, future studies should thus not only focus on the first event of incident MetS in a dataset but also consider change in status of MetS. In addition, in this analysis, we only examined the potential impact of PA on MetS. However, MetS is multifaceted and incidence of MetS, as well as PA pattern, may be influenced by other behavioral and/ or lifestyle-related factors such as nutrition (Huffman et al., 2014; Kassi et al., 2011; Kastorini et al., 2011; Malik et al., 2010; Myers, 2014).

Furthermore, future studies should not only focus on incident MetS as the outcome of interest, but also examine the association between PA with individual factors of MetS (i.e., waist circumference, glucose, HDL, triglycerides, blood pressure). Such approach would likely yield more detailed information on the potential impact of PA on various risk factors contributing to MetS. Furthermore, even though we conducted a longitudinal study to examine the association between PA (which was considered the predictor) and incident MetS (which was considered the outcome of interest), we cannot answer the question of cause and effect, and inverse causality may thus be possible. This means that participants who are in the early stages of MetS or have metabolic risk factors not yet severe enough to be classified as MetS, may be less likely to engage in sports-related PA at baseline or may be more likely to remain inactive during follow-up, and this may explain our observed associations between higher sports-related PA at baseline or continuous engagement in sports-related PA from baseline to follow-up, with a decreased risk of incident MetS. In addition, particularly in participants with loss to follow-up due to illness or death, or those with rather short follow-up period, the likelihood of observing changes in PA over time was low; which may have led to potential bias and reduced power for our statistical analyses. Similarly, the range of PA change differs between participants depending on the individual duration of follow-up which should also be taken into account when interpreting our data. Finally, occurrence of the event (i.e., incident MetS) may not have occurred during the data collection phase of this study, and participants may develop incident MetS after the observation period. Therefore, more research is needed to untangle the longitudinal associations between PA and incident MetS, and our study also needs to be confirmed by prospective studies conducted in other communities.

In conclusion, we here provide additional evidence of an association between sports-related PA and a decreased risk of incident MetS, i.e., being physically active at baseline with an amount of at least 75 minutes per week, as well as remaining physically active or even starting sports-related PA during follow-up were associated with a reduced risk of incident MetS. Our data shows that PA should be carried out at a rather high volume in order to achieve favorable health outcomes, and that habitual PA was not related to the risk of incident MetS. Our findings have implications for PA promotion in middle-aged adults aimed at increasing metabolic health, and underline the importance of structured PA health promotion programs and public health strategies, even at community-based levels.

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AUTHOR CONTRIBUTIONS

Each author has contributed, edited and approved the contents of the submitted paper. All authors had final approval of the submitted and published versions. LC wrote the first draft of the manuscript, conducted the statistical analyses and collected the data. JKR reviewed and edited the manuscript, and provided statistical consultation. SCES provided statistical consultation, collected the data, and reviewed and edited the manuscript. AD collected the data, and reviewed and edited the manuscript. DJ provided statistical consultation, and reviewed and edited the manuscript. KB and AW initiated the study, and reviewed and edited the manuscript.

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DATA AVAILABILITY

The datasets generated and analyzed for the current study are not publicly available due to the strict ethical standards as required by the ethics committee of the Karlsruhe Institute of Technology, Germany. However, data may be available from the corresponding author on reasonable request.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

All references of publication II are included in the list of references at the end of this thesis.

4 LONGITUDINAL ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND FIVE RISK FACTORS OF METABOLIC SYNDROME IN MIDDLE-AGED ADULTS IN GERMANY

Publication III: Longitudinal associations between physical activity and five risk factors of metabolic syndrome in middle-aged adults in Germany

Slightly modified version of the submitted manuscript.

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4.1 ABSTRACT

Aim: We examined the longitudinal association between (change in) physical activity (PA) with new onset of five risk factors of metabolic syndrome among 657 middle-aged adults (mean age 44.1 (SD 8.6) years) who were free of the respective outcome at baseline, in a longitudinal cohort study spanning over 29 years.

Methods: Levels of habitual PA and sports-related PA (sPA) were assessed by a self-reported questionnaire. Incident elevated waist circumference (WC), elevated triglycerides (TG), reduced high-density lipoprotein cholesterols (HDL), elevated blood pressure (BP), and elevated blood-glucose (BG) were assessed by physicians and by self-reported questionnaires. We calculated Cox proportional hazard ratio (HR) regressions and 95 % confidence intervals (CI).

Results: Over time, participants developed (cases of incident risk factor; mean (SD) follow-up time) elevated WC (234 cases; 12.3 (8.2) years), elevated TG (292 cases; 11.1 (7.8) years), reduced HDL (139 cases; 12.4 (8.1) years), elevated BP (185 cases; 11.4 (7.5) years), or elevated BG (47 cases; 14.2 (8.5) years). For PA variables at baseline, risk reductions ranging between 37 % and 42 % for reduced HDL levels were detected. Furthermore, higher levels of PA (≥ 16.6 METh per week) were associated with a 49 % elevated risk for incident elevated BP. Participants who increased PA levels over time, had risk reductions ranging between 38 % and 57 % for elevated WC, elevated TG and reduced HDL. Participants with stable high amounts of PA from baseline to follow-up had risk reductions ranging between 45 % and 87 % for incident reduced HDL and elevated BG.

Conclusion: PA at baseline, starting PA engagement, maintaining and increasing PA level over time are associated with favorable metabolic health outcomes.

4.2 INTRODUCTION

Elevated waist circumference (WC), elevated triglycerides (TG), reduced high-density lipoprotein cholesterols (HDL), elevated blood pressure (BP), and elevated blood-glucose (BG) are considered risk factors of metabolic syndrome (MetS) (Alberti et al., 2009). The prevalence of MetS, and individual risk factors of MetS has increased over the past decades (Saklayen, 2018). It is estimated that the prevalence of MetS worldwide ranges between 20-25 % in the adult population, and up to 80 % of diabetes patients are affected (Belete et al., 2021; do Vale Moreira et al., 2020; Saklayen, 2018). These numbers are alarming, particularly considering the economic impact of MetS on health care systems (Saklayen, 2018; Scholze et al., 2010). Therefore, it is critical to identify potential lifestyle-related factors that may decrease the risk of new onset of MetS.

Physical activity (PA) is known as a lifestyle-related factor to impact the metabolic system in general. On a physiological level, PA has an impact on cardiovascular (e.g., improvement in oxygen uptake and transport capacity; reduction of heart rate; increase in stroke volume), hemodynamic (e.g., improvement in blood flow; increase in blood clotting readiness), metabolic (e.g., increase in mitochondria volume; improvement of enzyme activity of the musculature; change of cholesterol composition by improvement of HDL-LDL ratio), and endocrinological systems (e.g., increase in catecholamines, cortisol, growth hormones), amongst others (Boström et al., 2012; Malm et al., 2019; Woll & Bös, 2004). Furthermore, on an endocrinological level, an increase in the exercise-induced hormone Irisin by the skeletal muscle, may cause an increase in energy expenditure by transforming white into brown fat cells (brown-in-white or brite cells), which is linked to an improvement in glucose homeostasis (Boström et al., 2012; Kokkinos, 2012). Due to the direct impact on bodily functions, PA has a positive impact on an individual's health, and may thus also have a favorable impact on the risk of new onset of individual MetS risk factors.

The World Health Organization (WHO) recommends engaging in at least 150 minutes of moderate to vigorous PA, or 75 minutes of vigorous-intensity PA per week, or an equivalent combination of moderate- and vigorous-intensity activity to achieve health benefits (World Health Organization, 2020), which is equivalent to at least 8.3-16.6 metabolic equivalent-hours (METh) per week (respectively 500-1000 MET-minutes per week) (U.S. Department of Health and Human Services, 2018).

Indeed, a growing body of research has reported a beneficial effect of PA on cardiometabolic risk factors, e.g., being physically active may reduce body weight and BP, elevate HDL, lower

TG, and improve insulin resistance (Cleven et al., 2020; Franklin, 2008; Myers, 2014; Myers et al., 2019; Pucci et al., 2017; Sallis et al., 2016). Studies have also shown that engaging in higher levels of PA is associated with a reduced risk for incident MetS (Cheriyath et al., 2010; He et al., 2014; Wilsgaard & Jacobsen, 2007; D. Zhang et al., 2017). As it is important to focus on MetS itself, contribution of PA to the risk of new onset of the respective individual risk factors should be considered as well. Longitudinal studies reporting the association between variables of PA and individual risk factors of MetS, combined within one analysis or dataset, are scarce. However, to date, studies focusing on the longitudinal associations between various PA measures with individual factors of MetS in large, population-based samples are missing.

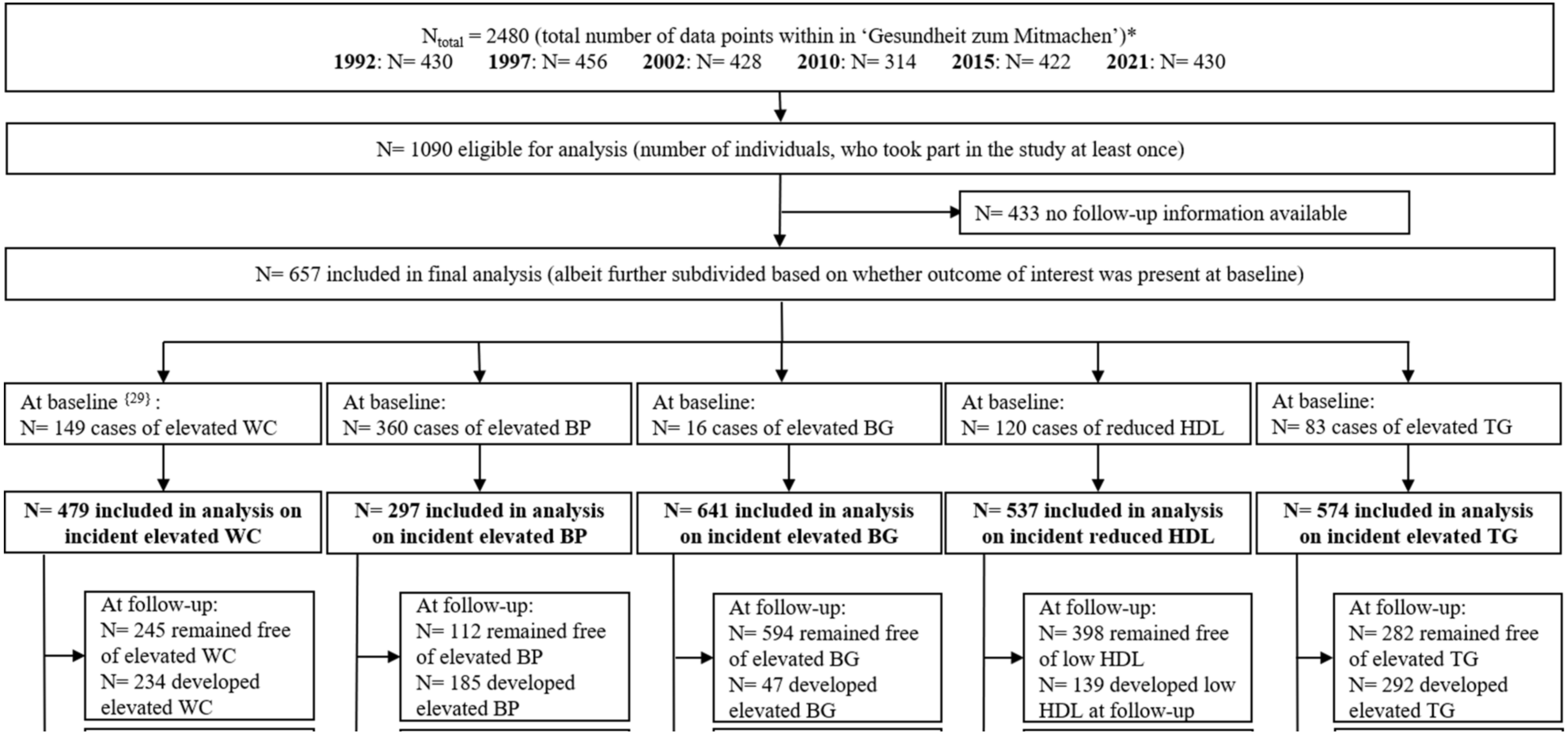
Therefore, the aim of this study was to examine the associations between various PA variables (i.e., habitual and sports-related PA, and change in PA behavior over time) and new onset of five different risk factors of MetS among middle-aged males and females from a community-based sample in South-Western Germany over a period of 29 years.

4.3 MATERIALS AND METHODS

4.3.1 STUDY DESIGN AND POPULATION

The research was conducted in the setting of the 'Gesundheit zum Mitmachen' study, which is an ongoing, community-based longitudinal cohort study of middle-aged and older adults living in the city of Bad Schönborn in South-Western Germany with six measurement points (1992, 1997, 2002, 2010, 2015, 2021). Details about the design and methods of the study have been described elsewhere (Tittlbach et al., 2017; Woll et al., 2004). The study was approved by the ethics committee of the Karlsruhe Institute of Technology (KIT), Germany, and was conducted in accordance with the Declaration of Helsinki. All methods were performed in accordance with pertinent guidelines and regulations.

Briefly, individuals residing in Bad Schönborn, Germany from five age strata (i.e., 35, 40, 45, 50, and 55 ± 2 years) were randomly selected from the local residents' registration offices and were invited to participate in the study in 1992 (initial sample). The response rate of the initial sample was 56 %. A non-responder telephone interview showed no significant differences in socioeconomic status (SES), physical health status, and PA between participants and invited non-participants except for migration background (Woll et al., 2004). Persons who participated in the study at least once were re-invited for every measurement point, and new samples of participants aged 33-37 years were included at each measurement point to prevent sample attrition.



Abbreviations: N = number of participants, WC = waist circumference, BP = blood pressure, BG = blood-glucose, HDL = high-density lipoprotein cholesterols, TG = triglycerides; { } = indicates numbers of cases with missing information. *Persons who participated in the study at least once were re-invited for every measurement point, and new participants were included at each measurement point to prevent sample attrition.

FIGURE 9: FLOW CHART OF STUDY PARTICIPATION (CHAPTER 4)

Participation in the study was voluntary and all participants provided written informed consent. At each of the six measurements points, participants provided information about self-rated health status, habitual and sports-related PA, and sociodemographic information through a self-reported questionnaire. All participants also underwent an objective health status examination conducted by a licensed physician, and had a blood sample drawn.

For the current analysis, from a total of 1090 individuals who participated in this study, we excluded participants with no longitudinal data information available (N = 433). A total of 657 participants were thus included in the statistical analysis. In a next step, for each of the five outcomes of interest, we excluded individuals with pre-existing risk factor at baseline for the respective analyses (please refer to Figure 9 for a flow chart of study participation).

4.3.2 Physical activity assessment (predictor variables)

All information regarding habitual and sports-related PA at baseline examination and follow-up was assessed by a self-reported questionnaire (test-retest reliability after two weeks: $r > .90$, $\alpha = .94$) (Jekauc, 2009).

Habitual PA. We calculated an index to quantify the amount of habitual PA at baseline (minutes per week) as indicator for recreational PA level (thus deliberately excluding sports activity participation) by creating a sum index that was derived from participants‘ self-reported information about daily minutes of walking, biking for transportation, as well as working in the household and gardening. For statistical analysis, the sample was divided into three groups (i.e., low: < 75 minutes per week, medium: 75-149 minutes per week, and high: ≥ 150 minutes/ week) based on the calculated index.

Sports-related PA. An index for the amount of sports-related PA at baseline was calculated from information provided by participants about frequency (i.e., number of weekly exercise sessions), duration (i.e., minutes per session), intensity (i.e., not very intense, moderately intense with some sweating, and highly intense with much sweating), and type of weekly sports-related PA (i.e., structured/ non structured; organized/ non-organized; e.g. playing soccer, tennis, running, hiking etc.) (Oja et al., 1994). For statistical analyses, the sample was divided into three groups (i.e., low: < 75 minutes per week, medium: 75-149 minutes per week, high: ≥ 150 minutes per week) to examine the influence of the cut-off points based on the global recommendation on PA level (World Health Organization, 2010). Furthermore, to consider the intensity level of the activity, every type of sport was assigned a specific MET-value (Ainsworth et al., 2011), and by multiplication with the time spent carrying out the respective activity, sports-related PA level in MET-hours (METh) per week at baseline was calculated. The global PA recommendation is equivalent to at least 8.3-16.6 METh per week (U.S. Department of Health and Human Services, 2018). Thus, for statistical analysis, the sample was divided into three groups (not active: < 8.3 METh per week, moderately active: 8.3-16.5 METh per week, highly active: ≥ 16.6 METh/ week) based on the sports-related PA level to examine the influence of thresholds based on the global recommendation.

Change of sports-related PA. To assess the change in minutes of sports-related PA per week, differences in PA level between baseline and the latest follow-up examination were calculated individually for each participant. Four categories by applying a 150 minutes per week threshold, based on WHO guidelines on physical activity and sedentary behavior (World Health Organization, 2020) were calculated. The four categories were stable inactive (i.e., individuals who continuously reported less than 150 minutes per week sports-related PA); quits activity (i.e., participants who reported more than 150 minutes per week sports-related PA at baseline but not follow-up); starts activity (i.e., individuals who reported less than 150 minutes per week sports-related PA at baseline but more than 150 minutes per week at follow-up); and stable active (i.e., participants who reported continuously more than 150 minutes per week of sports-related PA). Similarly, to assess the change in METh of sports-related PA, differences in METh level at baseline examination compared to the latest follow-up were calculated. By applying the threshold for METh recommended by the U.S. Department of Health and Human Services (2018), four groups were created: Stable low (i.e., individuals who continuously reported less than 16.6 METh per week sports-related PA), decreasing (i.e., participants who reported more than 16.6 METh per week sports-related PA at baseline but not at follow-up); increasing (i.e., individuals who reported less than 16.6 METh per week sports-related PA at baseline but more than 16.6 METh per week at follow-up); and stable high (i.e., participants who reported continuously more than 16.6 METh per week sports-related PA).

4.3.3 Individual factors of metabolic syndrome assessment (Outcomes of interest)

At baseline and each follow-up examination, the status of risk factors of MetS was assessed through examination by a licensed physician and corroborated by self-reported information on medication intake in the questionnaire. We defined having or developing new onset of risk factors of MetS, when the respective risk factors (i.e., elevated WC, elevated TG, reduced HDL, elevated BP, or elevated BG) were present at baseline examination or at follow-up (Alberti et al., 2009).

Elevated waist circumference. WC (in cm) was assessed at baseline and at each follow-up examination by standardized measurement. A participant was classified as having elevated WC when the WC was greater than 102 cm for males, and greater than 88 cm for females, respectively (National Institutes of Health, 1998; World Health Organization, 2000).

Blood lipids (triglycerides and high-density lipoprotein cholesterol). Blood lipids were assessed at baseline and at each follow-up examination by standardized measurement. Participants were classified as having elevated TG when the levels were greater than 150 mg/dL, and as having reduced HDL when the levels were lower than 40 mg/dL for males and lower than 50 mg/dL for females, respectively (Alberti et al., 2009). Furthermore, a participant was classified as having critical level of blood lipids (i.e., elevated TG or reduced HDL) if the diagnosis had been made previously by a physician, or if the participant was on medication for the respective condition, i.e., participants were asked: 'Do you take any medication to lower blood lipids?'

Elevated blood pressure. BP was assessed at baseline and each follow-up examination by standardized measurement. A participant was classified as having elevated BP if the systolic value was greater than 130 mmHg, or if the diastolic value was greater than 85 mmHg. Furthermore, a participant was classified as having elevated BP if hypertension diagnosis had been made previously by a physician, or if the participant was on BP medication (Alberti et al., 2009), i.e., participants were asked: 'Do you take any medication to lower your blood pressure?'

Elevated blood-glucose level. BG was determined by a physician at baseline and each follow-up examination based on BG levels (i.e., fasting BG level ≥ 100 mg/dL (Alberti et al., 2009), non-fasting BG level ≥ 200 mg/dL (Roden, 2016) for measurement points 1992 to 2015; and HbA1c ≥ 6,5 % in 2021 (Roden, 2016)). Furthermore, a participant was classified as having elevated BG level, if a diabetes diagnosis had been made previously by a physician or if the participant was on medication, i.e., participants were asked: 'Do you take any medication to lower blood-glucose levels?'

4.3.4 ASSESSMENT OF CONFOUNDERS

Traditional demographic variables (e.g., age and sex) were assessed though self-reported questionnaire. We also determined socio-economic status (SES) based on information provided by participants about formal education and professional status of themselves or their significant others (usually the spouse), if participants were not working. Four SES categories were used for statistical analysis, i.e., low, mid/ low, mid/ high and high SES (Hradil, 1987; Woll et al., 2004). Furthermore, comorbidities at study entry related to the risk factors of MetS (i.e., elevated WC, elevated TG, reduced HDL, elevated BP, and elevated BG, respectively) were determined.

4.3.5 Statistical analysis

Selected sociodemographic, behavioral, and health-related characteristics of the participants were used to characterize the cohort at baseline by using means (M) and standard deviation (SD). Cox proportional hazards regression models were calculated to examine the associations between various PA predictor variables (i.e., habitual and sports-related PA at baseline, and change in sports-related PA level from baseline to follow-up; variables were nominal coded or dummy coded), and the risk of new onset of a MetS risk factor. Only participants who were free of the respective outcome of interest at baseline, and had at least one follow-up measurement were included in the analysis. Date of study entry was used as baseline, and was determined individually for each participant. Follow-up time (in months) was calculated individually for each participant from baseline until the first event (i.e., incident elevated WC, elevated TG, reduced HDL, elevated BP, elevated BG) or loss to follow-up, whichever happened first. Missing values were treated as missing at random, which yielded in a pairwise deletion of cases with at least one missing value among either predictor or outcome variable for each analysis. Numbers of missing values are provided in the result table for each category of PA, respectively. We calculated Hazard Ratios (HR) and 95 % confidence intervals (CI) based on regression analyses for each category of PA as compared to the least active group which was always set as reference group (we also indicated the reference group in the results tables). For each predictor, we ran two sets of models: models adjusted for traditional confounding variables, i.e., age, sex and SES (Model 1), and models additionally adjusted for comorbidities at study entry related to the risk factors of MetS (i.e., elevated WC, reduced HDL, elevated TG, elevated BP, elevated BG) respectively. This means that, for example, in the models where the outcome of interest was elevated WC, we additionally adjusted for status of HDL, TG, BP and BG at study entry. However, it is recommended to do one adjustment per every 15 cases of incident event (per incident outcome of interest). Therefore, in order to avoid over-adjustment, we only report Model 1 for the outcome of interest blood-glucose, as we only had 47 participants who developed incident elevated blood-glucose levels during time under observation. Analyses were performed using SPSS software version 27, and using the conventional alpha level of 0.05 to determine statistical significance. A HR > 1.0 was considered as indicating an elevated risk for incident risk factors of MetS, a HR < 1.0 was considered as indicating a reduced risk for incident risk factors of MetS.

4.4 RESULTS

4.4.1 SAMPLE CHARACTERISTICS

Data were available on a total of 657 individuals with at least two study visits (i.e., baseline and at least one follow-up). Mean age at baseline was 44.1 (SD 8.6; range: 30-74) years, and 52.1 % of participants were female. Habitual PA was performed for a mean of 349.4 (SD 274.0) minutes per week. Sports-related PA was performed for a mean of 96.3 (SD 128.4) minutes per week, and with a mean of 11.6 (SD 15.5) METh per week, and it was most frequently performed for less than 75 minutes per week (53.3 %).

Sample size and demographics differed for the statistical analyses depending on the outcome of interest. Detailed information about baseline demographics of each study sample for the five different outcomes of interest (i.e., elevated WC, elevated TG, reduced HDL, elevated BP, elevated BG) are shown in Table 9.

TABLE 9: DEMOGRAPHICS OF STUDY PARTICIPANTS (STRATIFIED BY SEX) AT BASELINE FOR EACH OUTCOME OF INTEREST

	Outcomes of interest									
	Elevated WC (N = 479)		**Elevated TG (N = 574)**		**Reduced HDL (N = 537)**		**Elevated BP (N = 297)**		**Elevated BG (N = 641)**	
	male	female	male	female	male	female	male	female	male	female
Elevated WC, N (%)	-	-	50 (19.5){5}	60 (18.9){40}	48 (18.5){2}	46 (16.5){36}	10 (9.4){2}	29 (15.2){31}	62 (20.4){2}	67 (19.9){42}
Elevated TG, N (%)	44 (18.3)	18 (7.5)	-	-	34 (13.1)	12 (4.3)	21 (19.8)	10 (5.2)	58 (19.1)	24 (7.1)
Reduced HDL, N (%)	39 (16.3)	37 (15.5)	31 (12.1)	52 (16.4)	-	-	20 (18.9)	35 (18.3)	54 (17.8)	63 (18.7)
Elevated BP, N (%)	149 (62.1)	106 (44.4)	171 (66.8)	137 (43.1)	173 (66.8)	122 (43.9)	-	-	199 (65.5)	148 (43.9)
Elevated BG, N (%)	6 (2.5)	2 (0.8)	10 (3.9)	5 (1.6)	9 (3.5)	4 (1.4)	1 (0.9)	2 (1.0)	-	-
Cofounders										
N	240	239	256	318	259	278	106	191	304	337
Age [years], mean (SD)	43.3 (8.4)	44.0 (8.9)	44.5 (8.5)	44.1 (8.5)	44.4 (8.7)	44.1 (8.5)	41.0 (8.3)	41.9 (8.2)	44.3 (8.5)	43.8 (8.5)
SES, mean (SD)	3.2 (0.9){2}	2.9 (0.9){5}	3.1 (0.9){4}	2.8 (0.9){7}	3.1 (0.9){4}	2.8 (0.9){5}	3.2 (0.9){1}	2.9 (0.9){6}	3.1 (0.9){3}	2.8 (0.9){8}
Low (%)	4.6	10.0	5.1	10.7	5.4	10.1	2.8	7.9	5.9	10.1
Low/medium (%)	23.3	16.3	25.0	19.5	23.9	19.4	27.4	21.5	23.7	19.0
Medium/high (%)	24.2	44.4	24.6	43.4	26.6	44.6	19.8	41.4	25.3	43.6
High (%)	47.1	27.2	43.8	24.2	42.5	24.1	49.1	26.2	44.1	24.9
Predictors										
Habitual PA [min/week], mean (SD)	376.1 (302.9)	307.5 (239.1)	375.8 (305.5)	317.8 (233.9)	388.3 (313.8)	324.1 (237.9)	366.8 (288.0)	296.7 (209.2)	379.0 (310.5)	319.6 (230.1)
Low (< 75) (%)	4.6	5.9	6.3	5.3	5.4	5.4	1.9	6.3	5.3	5.0
Medium (75-149) (%)	22.5	26.8	21.1	23.9	22.4	24.1	23.6	25.7	21.7	22.8
High (≥ 150) (%)	72.9	67.4	72.7	70.8	72.2	70.5	74.5	68.1	73.0	72.2
Sports-related PA [min/week], mean (SD)	116.0 (148.4)	104.7 (126.8)	105.3 (144.4)	90.4 (119.2)	105.5 (142.6)	98.1 (125.8)	79.2 (93.8)	92.9 (121.5)	102.9 (137.9)	90.7 (120.1)
Inactive (< 75) (%)	47.1	47.7	50.4	55.0	51.0	53.2	56.6	53.4	52.0	55.5
Medium (75-149) (%)	26.3	25.1	25.8	20.8	25.1	20.1	26.4	23.0	24.0	20.5
High (≥ 150) (%)	26.7	27.2	23.8	24.2	23.9	26.6	17.0	23.6	24.0	24.0
Sports-related PA [METh/week], mean (SD)	14.1 (17.9)	12.3 (15.2){1}	12.4 (17.4)	10.9 (14.6){1}	12.9 (17.3)	12.0 (15.3){1}	9.5 (11.4)	10.5 (14.0){1}	12.4 (16.7)	10.9 (14.5){1}
Low (< 8.3) (%)	46.3	51.9	51.6	57.9	51.0	55.0	55.7	57.6	51.3	57.3
Medium (8.3-16.5) (%)	25.4	22.6	24.6	17.6	23.9	18.0	25.5	18.8	24.3	18.7
High (≥ 16.6) (%)	28.3	25.1	23.8	24.2	25.1	26.6	18.9	23.0	24.3	23.7

Abbreviations: N = sample size, SD = standard deviation, kg = kilograms, m = meters, cm = centimeters, min = minutes, PA = physical activity, METh = metabolic equivalent hours; WC = waist circumference, BP = blood pressure, BG = blood-glucose, HDL = high-density lipoprotein cholesterols, TG = triglycerides, { } = indicates number of N missing. Elevated waist circumference: ≥ 102 cm for males, ≥ 88 cm for females; elevated triglycerides: ≥ 150 mg/dL and/or specific medication; reduced HDL-cholesterols: < 40 mg/dL for males, < 50 mg/dL for females and/or specific medication; elevated blood pressure: systolic value ≥ 130 mmHg or diastolic value ≥ 85 mmHg and/or specific medication; elevated blood glucose: fasting blood-glucose level ≥ 100 mg/dL or non-fasting blood-glucose level ≥ 200 mg/dL or HbA1c ≥ 6,5% and/or specific medication.

4.4.2 *Association of PA with new onset of elevated waist circumference*

Of all participants included in the analysis, 224 (46.8 %) had one follow-up assessment, 101 (21.1 %) participants had two follow-up assessments, 74 (15.4 %) participants had three follow-up assessments, 49 (10.2 %) had four follow-up assessments, and 31 (6.5 %) participants had 5 follow-up assessments.

Table 10: Association between PA variables and the risk of incident elevated waist circumference

No. with incident elevated waist circumference (N=234, 48.9%)						
	No. at risk (N=479)	**No. incident elevated waist circumference (% of No. at risk)**	**Model 1 adjusted Hazard Ratio (95% CI)**	**p-value**	**Model 2 adjusted Hazard Ratio (95% CI)**	**p-value**
Habitual PA level at baseline [min/week]						
Low (< 75)	25	14 (2.9)	ref		ref	
Medium (75-149)	118	58 (12.1)	0.77 (0.42-1.41)	0.397	0.78 (0.42-1.43)	0.417
High (≥ 150)	336	162 (33.8)	0.73 (0.41-1.30)	0.284	0.72 (0.40-1.27)	0.253
Sports-related PA level at baseline [min/week]						
Low (< 75)	227	109 (22.8)	ref		ref	
Medium (75-149)	123	66 (13.8)	1.05 (0.77-1.44)	0.749	1.08 (0.79-1.49)	0.618
High (≥ 150)	129	59 (12.3)	0.92 (0.67-1.26)	0.594	0.88 (0.64-1.21)	0.424
Sports-related intensity level at baseline [METh/week] {1}						
Not intensively active (< 8.3)	235	110 (23.0)	ref		ref	
Moderately intensively active (8.3-16.5)	115	59 (12.3)	1.10 (0.80-1.52)	0.552	1.07 (0.78-1.48)	0.669
Highly intensively active (≥ 16.6)	128	65 (13.6)	1.09 (0.80-1.48)	0.593	1.06 (0.77-1.44)	0.725
Change in sports-related PA over time [min/week] {19}						
Stable inactive (< 150 to < 150)	234	115 (24.0)	ref		ref	
Quits activity (≥ 150 to < 150)	51	27 (5.6)	0.96 (0.63-1.47)	0.859	0.91 (0.59-1.39)	0.656
Starts activity (< 150 to ≥ 150)	111	58 (12.1)	0.75 (0.54-1.04)	0.084	0.78 (0.56-1.07)	0.123
Stable active (≥ 150 to ≥ 150)	64	26 (5.4)	0.69 (0.45-1.05)	0.084	0.66 (0.43-1.01)	0.057
Change in sports-related intensity level over time [METh/week] {4}						
Stable low (< 16.6 to < 16.6)	250	126 (26.3)	ref		ref	
Decreasing (≥ 16.6 to < 16.6)	47	29 (6.1)	1.32 (0.87-1.98)	0.188	1.37 (0.91-2.07)	0.130
Increasing (< 16.6 to ≥ 16.6)	98	42 (8.8)	**0.61 (0.43-0.88)**	**0.007***	**0.62 (0.45-0.92)**	**0.015**
Stable high (≥ 16.6 to ≥ 16.6)	80	35 (7.3)	0.72 (0.49-1.05)	0.084	0.70 (0.48-1.02)	0.060

Abbreviations: CI = confidence interval, METh = metabolic equivalent hours, min = minutes, N = number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status, WC = waist circumference. Model 1: adjusted for age, sex and SES; Model 2: adjusted for age, sex, SES, and comorbidities with regard to MetS risk factors at study entry. { } = indicates number of N missing. Significant values (p < 0.05) are in [bold]; significant values after Bonferroni correction for multiple testing are indicated by [*].

The mean (SD) times of follow-up assessments was of 2.1 (1.3). After a mean follow-up of 12.3 (SD 8.2, range 5-29) years, 234 (48.9 %) participants developed incident elevated WC (please refer to Figure 9) with 5872 person-years (sum of the time spans for each participant under observation).

Habitual and sports-related PA at baseline were not associated with the risk of incident elevated WC (please refer to Table 10). Increasing sports-related PA from < 16.6 METh per week at baseline to ≥ 16.6 METh per week at follow-up, was associated with a decreased risk of incident elevated WC (HR 0.62, 95 % CI 0.45-0.92, p = 0.015), compared to participants with a stable low sports-related PA level (Table 10).

4.4.3 Association of PA with incident elevated triglycerides

Of all participants included in the analysis, 242 (42.2 %) had one follow-up assessment, 133 (23.2 %) participants had two follow-up assessments, 95 (16.6 %) participants had three follow-up assessments, 64 (11.1 %) had four follow-up assessments, and 40 (7.0%) participants had 5 follow-up assessments. The mean (SD) times of follow-up assessments was of 2.2 (1.3). After a mean follow-up of 11.1 (SD 7.8, range 5-29) years, 292 (50.9 %) participants developed incident elevated TG (please refer to Figure 9) with 6360 person-years (sum of the time spans for each participant under observation).

Habitual and sports-related PA at baseline was not associated with the risk of incident elevated TG (please refer to Table 11). Participants who reported starting sports-related PA from < 150 minutes per week at baseline to ≥ 150 minutes per week at follow-up, had a decreased risk of incident elevated TG (HR 0.62, 95 % CI 0.44-0.88, p = 0.007) as compared to participants who remained continuously inactive. In addition, an increase in sports-related PA from < 16.6 METh per week at baseline to ≥ 16.6 METh per week at follow-up, was associated with a decreased risk of incident elevated TG (HR 0.63, 95 % CI 0.44-0.89, p = 0.009), compared to participants with a stable low sports-related PA level (Table 11).

TABLE 11: ASSOCIATION BETWEEN PA VARIABLES AND THE RISK OF INCIDENT ELEVATED TRIGLYCERIDES

No. with incident elevated triglycerides (N=292, 50.9%)						
	No. at risk (N=574)	**No. incident elevated triglycerides (% of No. at risk)**	**Model 1 adjusted Hazard Ratio (95% CI)**	**p-value**	**Model 2 adjusted Hazard Ratio (95% CI)**	**p-value**
Habitual PA level at baseline [min/week]						
Low (< 75)	33	19 (3.3)	ref		ref	
Medium (75-149)	130	58 (10.1)	0.98 (0.57-1.69)	0.947	1.24 (0.68-2.26)	0.489
High (≥ 150)	411	215 (37.5)	1.14 (0.70-1.88)	0.601	1.36 (0.78-2.35)	0.277
Sports-related PA level at baseline [min/week]						
Low (< 75)	304	162 (28.2)	ref		ref	
Medium (75-149)	132	68 (11.8)	0.92 (0.69-1.24)	0.596	1.04 (0.77-1.42)	0.793
High (≥ 150)	138	62 (10.8)	0.87 (0.65-1.17)	0.369	1.02 (0.74-1.40)	0.912
Sports-related intensity level at baseline [METh/week] {1}						
Not intensively active (< 8.3)	316	170 (29.6)	ref		ref	
Moderately intensively active (8.3-16.5)	119	62 (10.8)	0.97 (0.72-1.30)	0.818	1.06 (0.78-1.44)	0.733
Highly intensively active (≥ 16.6)	138	60 (10.5)	0.83 (0.62-1.12)	0.224	0.96 (0.70-1.33)	0.814
Change in sports-related PA over time [min/week] {28}						
Stable inactive (< 150 to < 150)	296	167 (29.1)	ref		ref	
Quits activity (≥ 150 to < 150)	52	29 (5.1)	0.95 (0.64-1.41)	0.800	1.08 (0.72-1.63)	0.705
Starts activity (< 150 to ≥ 150)	119	50 (8.7)	**0.62 (0.45-0.85)**	**0.003***	**0.62 (0.44-0.88)**	**0.007***
Stable active (≥ 150 to ≥ 150)	79	36 (6.3)	0.76 (0.53-1.10)	0.141	0.87 (0.59-1.29)	0.484
Change in sports-related intensity level over time [METh/week] {13}						
Stable low (< 16.6 to < 16.6)	318	181 (31.5)	ref		ref	
Decreasing (≥ 16.6 to < 16.6)	58	29 (5.1)	0.88 (0.59-1.31)	0.530	1.05 (0.69-1.59)	0.823
Increasing (< 16.6 to ≥ 16.6)	110	45 (7.8)	**0.58 (0.42-0.81)**	**0.001***	**0.63 (0.44-0.89)**	**0.009***
Stable high (≥ 16.6 to ≥ 16.6)	75	30 (5.2)	**0.66 (0.45-0.98)**	**0.037**	0.76 (0.50-1.14)	0.182

Abbreviations: CI = confidence interval, METh = metabolic equivalent hours, min = minutes, N = number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status, TG = triglycerides. Model 1: adjusted for age, sex and SES; Model 2: adjusted for age, sex, SES, and comorbidities with regard to MetS risk factors at study entry. { } = indicates number of N missing. Significant values (p < 0.05) are in [bold]; significant values after Bonferroni correction for multiple testing are indicated by [*].

4.4.4 ASSOCIATION OF PA WITH INCIDENT REDUCED HIGH-DENSITY LIPOPROTEIN CHOLESTEROLS

Of all participants included in the analysis, 248 (46.2 %) had one follow-up assessment, 108 (20.1 %) participants had two follow-up assessments, 88 (16.4 %) participants had three follow-up assessments, 54 (10.1 %) had four follow-up assessments, and 39 (7.3 %) participants had 5 follow-up assessments. The mean (SD) times of follow-up assessments was of 2.1 (1.3). After a mean follow-up of 12.4 (SD 8.1, range 5-29) years, 139 (25.9 %) participants developed incident reduced HDL (please refer to Figure 9) with 6661 person-years (sum of the time spans for each participant under observation).

Habitual PA was not associated with the risk of incident reduced HDL. Engaging in sports-related PA between 75-149 minutes per week at baseline was associated with a decreased risk of incident reduced HDL (HR 0.59, 95 % CI 0.37-0.95, p = 0.031), and engaging in high sports-related PA level (≥ 150 minutes per week) was also associated with a decreased risk of incident reduced HDL (HR 0.63, 95 % CI 0.40-0.99, p = 0.048), compared to sports-related PA carried out for less than 75 minutes per week (please refer to Table 4). With regard to the METh of sports-related PA, being physically active with more than 16.6 METh per week at baseline was associated with a decreased risk of incident reduced HDL (HR 0.58, 95 % CI 0.36-0.93, p = 0.024), compared to participants who were not active (Table 12).

With regard to change in sports-related PA behavior, participants who reported starting to engage in sports-related PA from < 150 minutes per week at baseline to ≥ 150 minutes per week at follow-up, had a decreased risk of incident reduced HDL (HR 0.43, 95 % CI 0.25-0.74, p = 0.002) as compared to participants who remained continuously inactive. In addition, increasing sports-related PA from < 16.6 METh per week at baseline to ≥ 16.6 METh per week at follow-up, was associated with a decreased risk of incident reduced HDL (HR 0.43, 95 % CI 0.24-0.77, p = 0.004), and for participants who reported a stable high sports-related PA (stable ≥ 16.6 METh per week), a decreased risk of incident reduced HDL (HR 0.55, 95 % CI 0.31-0.97, p = 0.040) was found, compared to being stable inactive (Table 12).

TABLE 12: ASSOCIATION BETWEEN PA VARIABLES AND THE RISK OF INCIDENT REDUCED HIGH-DENSITY LIPOPROTEIN CHOLESTEROLS

No. with incident reduced HDL (N=139, 25.9%)						
	No. at risk (N=537)	**No. incident reduced HDL (% of No. at risk)**	**Model 1 adjusted Hazard Ratio (95% CI)**	**p-value**	**Model 2 adjusted Hazard Ratio (95% CI)**	**p-value**
Habitual PA level at baseline [min/week]						
Low (< 75)	29	11 (1.9)	ref		ref	
Medium (75-149)	125	31 (5.4)	0.85 (0.41-1.74)	0.648	0.86 (0.41-1.79)	0.683
High (≥ 150)	383	97 (16.9)	0.77 (0.40-1.49)	0.442	0.72 (0.37-1.40)	0.332
Sports-related PA level at baseline [min/week]						
Low (< 75)	280	87 (15.2)	ref		ref	
Medium (75-149)	121	26 (4.5)	**0.61 (0.39-0.96)**	**0.034**	**0.59 (0.37-0.95)**	**0.031**
High (≥ 150)	136	26 (4.5)	**0.63 (0.41-0.98)**	**0.041**	**0.63 (0.40-0.99)**	**0.048**
Sports-related intensity level at baseline [METh/week] {1}						
Not intensively active (< 8.3)	285	88 (15.4)	ref		ref	
Moderately intensively active (8.3-16.5)	112	26 (4.5)	0.72 (0.46-1.13)	0.149	0.68 (0.43-1.09)	0.107
Highly intensively active (≥ 16.6)	139	25 (4.4)	**0.59 (0.37-0.93)**	**0.022**	**0.58 (0.36-0.93)**	**0.024**
Change in sports-related PA over time [min/week] {24}						
Stable inactive (< 150 to < 150)	276	86 (15.0)	ref		ref	
Quits activity (≥ 150 to < 150)	38	8 (1.4)	0.61 (0.30-1.27)	0.189	0.66 (0.32-1.38)	0.269
Starts activity (< 150 to ≥ 150)	120	23 (4.0)	**0.54 (0.34-0.87)**	**0.011**	**0.43 (0.25-0.74)**	**0.002***
Stable active (≥ 150 to ≥ 150)	79	18 (3.1)	0.74 (0.44-1.23)	0.245	0.67 (0.39-1.16)	0.156
Change in sports-related intensity level over time [METh/week] {11 }						
Stable low (< 16.6 to < 16.6)	86	92 (16.1)	ref		ref	
Decreasing (≥ 16.6 to < 16.6)	101	9 (1.6)	0.56 (0.27-1.15)	0.114	0.62 (0.30-1.28)	0.193
Increasing (< 16.6 to ≥ 16.6)	50	17 (3.0)	**0.48 (0.28-0.81)**	**0.006***	**0.43 (0.24-0.77)**	**0.004***
Stable high (≥ 16.6 to ≥ 16.6)	289	16 (2.8)	**0.57 (0.33-0.98)**	**0.040**	**0.55 (0.31-0.97)**	**0.040**

Abbreviations: CI = confidence interval, METh = metabolic equivalent hours, HDL = high-density lipoprotein cholesterols, min = minutes, N = number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status. Model 1: adjusted for age, sex and SES; Model 2: adjusted for age, sex, SES, and comorbidities with regard to MetS risk factors at study entry. { } = indicates number of N missing. Significant values ($p < 0.05$) are in [bold]; significant values after Bonferroni correction for multiple testing are indicated by [*].

4.4.5 *ASSOCIATION OF PA WITH INCIDENT ELEVATED BLOOD PRESSURE*

Of all participants included in the analysis, 127 (42.8 %) had one follow-up assessment, 67 (22.6 %) participants had two follow-up assessments, 46 (15.5 %) participants had three follow-up assessments, 39 (13.1 %) had four follow-up assessments, and 18 (6.1 %) participants had 5 follow-up assessments. The mean (SD) times of follow-up assessments was of 2.2 (1.3). After a mean follow-up of 11.4 (SD 7.5, range 5-29) years, 185 (62.3 %) participants developed incident elevated BP (please refer to Figure 9) with 3387 person-years (sum of the time spans for each participant under observation).

Habitual PA was not associated with the risk of incident elevated BP in our data set (please refer to Table 13). With regard to METh of sports-related PA, being physically active with more than 16.6 METh per week at baseline was associated with an increased risk of incident elevated BP (HR 1.49, 95 % CI 1.01-2.20, p = 0.044), compared to participants who were not active.

Participants who reported cutting down sports-related PA from ≥ 150 minutes per week at baseline to < 150 minutes per week at follow-up, had an increased risk of incident elevated BP (HR 1.68, 95 % CI 1.01-2.80, p = 0.046) as compared to participants who remained continuously inactive (Table 13).

TABLE 13: ASSOCIATION BETWEEN PA VARIABLES AND THE RISK OF INCIDENT ELEVATED BLOOD PRESSURE

No. with incident elevated BP (N=185, 62.3%)						
	No. at risk (N=297)	**No. incident elevated BP (% of No. at risk)**	**Model 1 adjusted Hazard Ratio (95% CI)**	**p-value**	**Model 2 adjusted Hazard Ratio (95% CI)**	**p-value**
Habitual PA level at baseline [min/week]						
Low (< 75)	14	8 (2.7)	ref		ref	
Medium (75-149)	74	44 (14.8)	1.23 (0.58-2.62)	0.597	1.00 (0.42-2.40)	0.995
High (≥ 150)	209	133 (44.8)	1.23 (0.59-2.54)	0.583	1.056 (0.46-2.45)	0.899
Sports-related PA level at baseline [min/week]						
Low (< 75)	162	98 (33.0)	ref		ref	
Medium (75-149)	72	45 (15.2)	1.09 (0.75-1.57)	0.652	1.11 (0.75-1.65)	0.607
High (≥ 150)	63	42 (14.1)	1.30 (0.90-1.88)	0.163	1.40 (0.94-2.09)	0.098
Sports-related intensity level at baseline [METh/week] {1}						
Not intensively active (< 8.3)	169	95 (32.0)	ref		ref	
Moderately intensively active (8.3-16.5)	63	45 (15.2)	1.34 (0.93-1.92)	0.118	1.26 (0.86-1.85)	0.241
Highly intensively active (≥ 16.6)	64	45 (15.2)	1.42 (0.99-2.03)	0.058	**1.49 (1.01-2.20)**	**0.044**
Change in sports-related PA over time [min/week] {12}						
Stable inactive (< 150 to < 150)	171	102 (34.3)	ref		ref	
Quits activity (≥ 150 to < 150)	26	20 (6.7)	**1.65 (1.01-2.69)**	**0.046**	**1.68 (1.01-2.80)**	**0.046**
Starts activity (< 150 to ≥ 150)	59	38 (12.8)	0.75 (0.51-1.10)	0.142	0.69 (0.45-1.06)	0.090
Stable active (≥ 150 to ≥ 150)	29	18 (6.1)	0.92 (0.55-1.53)	0.737	0.92 (0.52-1.63)	0.775
Change in sports-related intensity level over time [METh/week] {3}						
Stable low (< 16.6 to < 16.6)	176	103 (34.7)	ref		ref	
Decreasing (≥ 16.6 to < 16.6)	30	22 (7.4)	1.47 (0.92-2.34)	0.106	1.52 (0.92-2.50)	0.101
Increasing (< 16.6 to ≥ 16.6)	55	36 (12.1)	0.74 (0.50-1.10)	0.137	0.74 (0.49-1.13)	0.158
Stable high (≥ 16.6 to ≥ 16.6)	33	23 (7.7)	1.03 (0.65-1.63)	0.904	1.11 (0.68-1.81)	0.668

Abbreviations: BP = blood pressure, CI = confidence interval, METh = metabolic equivalent hours, min = minutes, N = number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status. Model 1: adjusted for age, sex and SES; Model 2: adjusted for age, sex, SES, and comorbidities with regard to MetS risk factors at study entry. { } = indicates number of N missing. Significant values ($p < 0.05$) are in [bold]; significant values after Bonferroni correction for multiple testing are indicated by [*].

4.4.6 Association of PA with incident elevated blood-glucose

Of all participants included in the analysis, 283 (44.1 %) had one follow-up assessment, 145 (22.6 %) participants had two follow-up assessments, 108 (16.8 %) participants had three follow-up assessments, 64 (10.0 %) had four follow-up assessments, and 41 (6.4 %) participants had 5 follow-up assessments. The mean (SD) times of follow-up assessments was of 2.1 (1.3). After a mean follow-up of 14.2 (SD 8.5, range 5-29) years, 47 (7.3 %) participants developed incident elevated BG (please refer to Figure 9) with 9082 person-years (sum of the time spans for each participant under observation).

Table 14: Association between PA variables and the risk of incident elevated blood- glucose

No. with incident elevated BG (N=47, 7.3%)				
	No. at risk (N=641)	**No. incident elevated BG (% of No. at risk)**	**Model 1 adjusted Hazard Ratio (95% CI)**	**p-value**
Habitual PA level at baseline [min/week]				
Low (< 75)	33	2 (0.3)	ref	
Medium (75-149)	143	11 (1.7)	2.12 (0.46-9.85)	0.338
High (≥ 150)	465	34 (5.3)	1.39 (0.33-5.82)	0.656
Sports-related PA level at baseline [min/week]				
Low (< 75)	345	31 (4.8)	ref	
Medium (75-149)	142	10 (1.6)	0.97 (0.46-2.06)	0.942
High (≥ 150)	154	6 (0.9)	0.54 (0.22-1.32)	0.176
Sports-related intensity level at baseline [METh/week] {1}				
Not intensively active (< 8.3)	349	31 (4.8)	ref	
Moderately intensively active (8.3-16.5)	137	11 (1.7)	1.13 (0.55-2.28)	0.745
Highly intensively active (≥ 16.6)	154	5 (0.7)	0.50 (0.19-1.30)	0.154
Change in sports-related PA over time [min/week] {26}				
Stable inactive (< 150 to < 150)	333	34 (5.3)	ref	
Quits activity (≥ 150 to < 150)	52	5 (0.7)	0.97 (0.38-2.50)	0.950
Starts activity (< 150 to ≥ 150)	144	6 (0.9)	0.43 (0.17-1.04)	0.062
Stable active (≥ 150 to ≥ 150)	86	1 (0.1)	**0.13 (0.02-0.92)**	**0.042**
Change in sports-related intensity level over time [METh/week] {6}				
Stable low (< 16.6 to < 16.6)	348	32 (5.0)	ref	
Decreasing (≥ 16.6 to < 16.6)	54	4 (0.6)	1.03 (0.36-2.95)	0.962
Increasing (< 16.6 to ≥ 16.6)	135	10 (1.6)	0.76 (0.36-1.58)	0.457
Stable high (≥ 16.6 to ≥ 16.6)	98	1 (0.1)	**0.13 (0.02-0.99)**	**0.049**

Abbreviations: BG = blood-glucose, CI = confidence interval, METh = metabolic equivalent hours, min = minutes, N = number of participants, No. = Number, PA = physical activity, ref = reference group, SES = socio-economic status. Model 1: adjusted for age, sex und SES. Model 2 not reported due to small sample size of N = 47 which does not allow for adjustment of more than three confounding variables. { } = indicates number of N missing. Significant values (p < 0.05) are in [bold]; significant values after Bonferroni correction for multiple testing are indicated by [*].

Habitual and sports-related PA were not associated with the risk of incident elevated BG (please refer to Table 14). For participants who were stable active (stable ≥ 150 minutes per week from baseline to follow-up), there was a decreased risk of incident elevated BG (HR 0.13, 95 % CI 0.02-0.92, p = 0.042) compared to participants who were stable inactive. In addition, for participants who reported a stable high sports-related PA (stable ≥ 16.6 METh per week from baseline to follow-up), there was a decreased risk of incident elevated BG (HR 0.13, 95 % CI 0.02-0.99, $p = 0.049$) compared to participants with a stable low sports-related PA level (Table 14).

4.5 Discussion

The aim of this study was to examine the associations between various PA variables and new onset of five different risk factors of MetS among middle-aged males and females from a community-based sample in South-Western Germany over a period of 29 years.

Our study adds to the growing body of research on the association between PA levels and risk reduction of new onset of risk factors of MetS. Higher PA levels at baseline were associated with a decreased risk of new onset of reduced HDL, with risk reductions ranging between 37 to 42 % depending on the PA variable. To our surprise, we observed a 49 % increased risk of incident elevated BP in association with higher PA levels. In our data, there was no association between baseline PA levels and WC, TG or BG.

With regard to the association between changes in PA levels from baseline to follow-up, and risk of new onset of risk factors of MetS, we observed several statistically significant associations. For example, engaging in stable high sports-related PA from baseline to follow-up was associated with a 87 % decreased risk of incident elevated BG for PA levels of 150 minutes or ≥ 16.6 METh per week. Furthermore, stable high levels of sports-related PA of METh from baseline to follow-up was associated with a 45 % decreased risk of incident reduced HDL. In addition, favorable changes in sports-related PA levels from baseline to follow-up, were associated with various risk reductions, ranging from a 37 % decreased risk of incident elevated TG, to a 57 % decreased risk of incident reduced HDL, and a 38 % decreased risk for elevated WC. In contrast, reducing sports-related PA levels to below 150 minutes per week over time was associated with a 68 % increased risk of incident elevated BP.

In general, we observed that various PA variables were associated with decreased risks of new onset of elevated TG, and reduced HDL. This is in line with previous research. For example, longitudinal studies reported that leisure time PA was associated with higher circulating levels of HDL (Hernáez et al., 2021), and that an higher baseline levels of PA were associated with increases in HDL in all participants, whereas decreases in TG were only found in White study participants (Monda et al., 2009). Of note, in our study, we could show that particularly increasing PA (minutes and METh) over time seem to be beneficial to reduce the risk of new onset of elevated TG levels or reduced HDL which is also consistent with previous reports (e.g. Aadahl et al., 2009).

Several studies reported associations between PA levels and a decreased risk of incident elevated BG (Carlsson et al., 2013; Shi et al., 2013; Williams & Thompson, 2013) or diabetes (Y. Zhang et al., 2020). Whereas, we could not find an association between baseline PA levels but favorable change in PA over and decreased risk of incident elevated BG which is also in line with prior studies (e.g. Jefferis et al., 2012; Leskinen et al., 2018). Thus, we conclude that particularly stable or increasing engagement in PA over longer periods of time is beneficial in reducing the risk of new onset of elevated BG levels.

In our data, PA does not appear to be associated with WC. In contrast, a study by Cardenas et al. reported an inverse association of leisure time PA with WC, abdominal obesity and BMI (Cárdenas-Fuentes et al., 2018). With regard to changes in PA levels over time, a large Asian cohort study reported that an increase in PA was associated with lower abdominal obesity (Martinez-Gomez et al., 2020). However, a comparison between our research with other longitudinal studies is questionable, as most prior studies focused either on body weight change/ obesity as outcome of interest (Wilks et al., 2011), or on waist circumference as predictor variable (Rhee et al., 2018), rather than outcome of interest like we did. Thus, more research on the longitudinal association between PA and risk of incident elevated WC is warranted, and researchers may also want to consider other factors such as nutrition which may play an important role on the association between PA and WC (e.g. Newby et al., 2003).

Also, to our surprise, our data point towards an increased risk of incident elevated BP in association with PA, particularly of higher amounts of METh. Indeed, previous studies on the association between PA levels and BP as outcome of interest have also reported conflicting results. For example, a study from Mexico reported an increased risk of hypertension in participants who were physically inactive compared to those who were highly active but found no association between total PA and hypertension (Medina et al., 2018), whereas another study found no significant association between PA and risk of hypertension (Lu et al., 2015). Furthermore, other studies reported that higher baseline levels as well as stable PA levels are associated with lower risk of incident hypertension (Bakker et al., 2018; Cai et al., 2021; Williams & Thompson, 2013). In contrast to these reports, our results showed an increased risk of elevated BP for participants who are intensively active compared to those who are inactive. However, differences between our study and previous studies may pertain to study samples and methodology, such as assessment of PA. Also, more research is needed to untangle the potential mechanisms that may underlie an association between PA and reduced or increased risk of new onset of risk factors of MetS.

Our research showed that, in addition to baseline PA, particularly PA engagement over time may be crucial to elicit potential beneficial effects on cardiometabolic health. As stated in the introduction, underlying physiological effects of PA may impact the metabolic system. In addition to its direct impact on the body, a certain lifestyle (i.e., healthy nutrition, sufficient engagement in PA) may have an impact on human body's health in the long-term (Saklayen, 2018). With regard to potential health benefits, PA engagement on the one hand, and stability of sports participation on the other hand appear to be important factors (i.e. Friedman et al., 2008; Mertens et al., 2017). Additionally, future research may need to take into account quantity and quality of PA, such as type and intensity of PA over time, and preferably across the lifespan. Based on our findings, we hypothesize that maintaining or even increasing continuous engagement in sports-related PA across the lifespan may be most effective in order to achieve desirable health benefits with regard to cardiometabolic risk reduction.

A major strength of our study is the longitudinal design with a long follow-up period of 29 years. To the best of our knowledge, only few studies exist with such a long follow-up time (e.g., Harvard Alumni Study (Paffenbarger et al., 1978), Framingham Heart Study (Dawber et al., 1951), National Health and Nutritional Examination Survey (Barkley, 2008), Nurses' Health Study (Belanger et al., 1978)). In addition to previous studies, our analysis focused not only on sports-related PA at baseline, but also considered habitual activity and change in sports-related PA during follow-up. Furthermore, self-reported health status of participants was augmented by a health examination performed by a licensed physician.

Limitations of our study pertain to the rather small sample of participants with predominantly medium to high SES. Thus, our results may not be generalizable to communities of middle-aged adults with lower SES. In addition, PA was assessed by a self-reported questionnaire, which may be prone to recall bias, i.e., PA may have been over- or underestimated by participants. However, the questionnaire used in our study has been tested for reliability (test-reliability for two weeks $r > .90$) and internal consistency ($\alpha = .94$) (Jekauc, 2009). Furthermore, we did not examine changes in PA between childhood or youth and adulthood, or between early and middle adulthood. It is known that participation in PA varies across the lifespan, e.g., sports behavior is rather stable from childhood to youth (Telama et al., 2005), whereas PA behavior in adulthood is instable (Gordon-Larsen et al., 2004). Therefore, an objective assessment of PA behavior (i.e., using accelerometry) would add beneficial information about PA and should be considered in future research. Furthermore, our results are not adjusted for multiple comparison, and this may lead to potential risk of bias. Therefore, a post-hoc Bonferroni correction can be applied to adjust p-values for multiple testing according to the formula (adjusted p-value = 0.05/ number of tests) (Armstrong, 2014). Thus, the adjusted p-value after Bonferroni Correction is 0.01 (= 0.05/ 5), for each outcome of interest respectively. Results that remained significant after correction are indicated by * in the result tables (please refer to Tables 10-14). This applies to the associations between changing PA (increasing PA from below to more than 150 minutes/ 16.6 METh per week) and incident reduced HDL and elevated TG. In addition, with regard to change in PA behavior as predictor variable in our analyses, we only considered the first and latest information on PA available in our datasets. Thus, potential fluctuations in PA behavior between other measurements are not reflected which may have led to biased findings. Therefore, further analyses should consider other statistical analyses to better account for fluctuations over time such as latent growth curve analyses.

In our study, we considered the first occurrence of onset of risk factors of MetS as the outcome of interest. However, by definition, the status of these five risk factors may fluctuate over time in participants, particularly as we had several measurement points. As this sample selection definition may led to potential bias, future studies should thus not only focus on the first event of incident risk factor of MetS in a dataset, but also consider change in status of risk factors of MetS. Due to the focus on risk factors of MetS (i.e., WC, HDL, TG, BP or BG) it is possible to predict incident MetS (Heidari et al., 2010). Furthermore, we did not examine the association between risk factors and their dependence within each other. Thus, in addition to calculating HRs, future studies may explore a different statistical approach, e.g. linear-mixed modelling. In addition, in our analysis, we only examined the potential impact of PA on MetS risk factors. However, MetS is multifaceted and incidence of MetS risk factors, as well as PA pattern, may be influenced by other behavioral and/ or lifestyle-related variables such as nutrition (Huffman et al., 2014; Kassi et al., 2011; Kastorini et al., 2011; Malik et al., 2010; Myers, 2014) or fitness (Katzmarzyk et al., 2007; Tittlbach et al., 2017). Finally, even though we conducted a longitudinal study to examine the association between PA (which was considered the predictor) and incident outcome of interests, we cannot answer the question of cause and effect, and inverse causality may thus be possible. Therefore, more research is needed to untangle the longitudinal associations between PA and incident risk factors of MetS, and our study also needs to be confirmed by prospective studies conducted in other communities.

In conclusion, our data shows that engagement in PA, particularly at medium or high levels, as well as starting PA engagement, or maintaining and increasing PA levels over time are associated with decreased risk of new onset of MetS risk factors, particularly elevated TG, reduced HDL, elevated WC, and elevated BG. These findings have implications for PA promotion in middle-aged adults aimed at increasing metabolic health, and underline the importance of structured PA health promotion programs and public health strategies, even at community-based levels.

CONFLICT OF INTEREST

The authors declare no competing interest.

AUTHOR CONTRIBUTIONS

Each author has contributed, edited and approved the contents of the submitted paper. All authors had final approval of the submitted and published versions. LC wrote the first draft of the manuscript, conducted the statistical analyses and collected the data. AD collected the data, and reviewed and edited the manuscript. JKR reviewed and edited the manuscript, and provided statistical consultation. SCES provided statistical consultation, collected the data, and reviewed and edited the manuscript. DJ provided statistical consultation, and reviewed and edited the manuscript. KB and AW initiated the study, and reviewed and edited the manuscript.

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All references of publication III are included in the list of references at the end of this thesis.

5 GENERAL DISCUSSION

This thesis focused on the outcomes of incident NCDs (i.e. MetS and its five individual risk factors) as predicted by different PA variables. Three research questions (*Question 1-3*) were addressed through three publications (*Publication I-III*). Overall, the findings reported in this thesis provide further evidence of a favorable association between PA and cardiometabolic health. In particular, this research showed that

(a) several longitudinal studies exist, that reported associations between PA and decreased risks of incident obesity, coronary heart disease, diabetes but not hypertension (Cleven et al., 2020);

(b) initial sports-related PA, but not necessarily habitual PA, is associated with a reduced risk of incident MetS in middle-aged adults (Cleven et al., 2022);

(c) increasing or maintaining high levels of sports-related PA are associated with a reduced risk of incident MetS (Cleven et al., 2022);

(d) sports participation at study entry, particularly high levels of sports-related PA at baseline, but not habitual PA, are associated with a reduced risk of new onset of reduced HDL-cholesterols (Cleven et al., 2023);

(e) starting and maintaining high levels of sports-related PA are associated with a reduced risk of onset of elevated WC, TG, BG levels, and reduced HDL, but not elevated BP (Cleven et al., 2023);

and (f) higher sports-related PA levels at baseline and quitting sports-related PA from baseline to follow-up were associated with an elevated risk for new onset of elevated BP (Cleven et al., 2023).

Over the past decades, the scientific community has increased its efforts to gain a better understanding of the associations between PA behavior and various health outcomes, including but not limited to risk factors of MetS. The findings of this thesis support existing evidence of health promotion through sports-related PA. In the past, randomized-controlled trials, cross-sectional and longitudinal studies were conducted, indicating an overall favorable health benefit of PA on metabolic risk factors (i.e. Alkaf et al., 2021; Amagasa et al., 2018; Hadgraft et al., 2021; Patnode et al., 2017; Sui et al., 2017; Wilsgaard & Jacobsen, 2007). Those findings are supported by published reviews as well as meta-analyses (He et al., 2014; D. Zhang et al., 2017), highlighting the importance of PA promotion for health benefits.

A major strength of the analyses as part of this thesis is the longitudinal design with a long follow-up period of 29 years. To the best of our knowledge, only a few studies exist with such a long follow-up time (e.g., Harvard Alumni Study (Paffenbarger et al., 1978), Framingham Heart Study (Dawber et al., 1951), National Health and Nutritional Examination Survey (Barkley, 2008), Nurses' Health Study (Belanger et al., 1978)). In addition to previous studies, the analyses focused not only on sports-related PA at baseline, but also considered habitual activity and change in sports-related PA during follow-up as predictor variables. Furthermore, self-reported health status of participants was augmented by a health examination performed by a licensed physician.

However, to gain a better impression of this work, it is important to consider some limitations of the articles included in this thesis. In addition to the limitations mentioned in the three publications, the following further limitations should be considered.

For the analyses presented in publication II and III, the initial sample size was reduced by design (i.e. exclusion criteria), and only those participants who were free of the respective outcome of interest at baseline were included in the analyses. This reduction of sample size may have led to an important loss of information about the health status of participants. To gather the maximum statistical power, additional analyses should be conducted, to include all participants independently of their health status at study entry and throughout follow-up. Linear mixed-models may be a suitable approach to converge problems of sample bias and may thus be considered in future analyses.

Furthermore, the results of publication II were not adjusted for multiple comparison. To this end, a post-hoc Bonferroni correction can be applied to adjust p-values for multiple testing according to the formula (adjusted p-value = 0.05/ number of tests) (Armstrong, 2014). The adjusted p-value for publication II after Bonferroni correction is 0.006 (= 0.05/ 9). Thus, for adjusted Model 2, increasing MET-hours from below 16.6 to higher than 16.6 per week from baseline to follow-up remained significant (HR 0.47, 95 % CI 0.31-0.71, p = .001). Adjusted p-value after Bonferroni correction ($p_{adjusted} = 0.01$ ($\triangleq$ 0.05/ 5)) in publication III were reported in the discussion section. Thus, this applies to the associations between changing PA (increasing PA from below to more than 150 minutes/ 16.6 METh per week) and incident reduced HDL and elevated TG.

The model of the associations between physical behavior, health-related fitness, and health status by Bouchard et al. (2012) was used to explain the association between PA as predictor variables, and MetS as well as MetS risk factors as outcomes of interest in this thesis (Figure 4). The underlying multifaceted physiological effects of PA have an impact on the metabolic system and the human body overall. It is well-established that PA has an impact on cardiovascular, hemodynamic, metabolic, and endocrinological systems, amongst others (Boström et al., 2012; Kokkinos, 2012; Malm et al., 2019; Woll & Bös, 2004). Due to the continuous exposure to PA, and its multifaceted influence on the body, the body is adapting physiologically, and energy expenditure is positively influenced (Miko et al., 2020). However, those adaptions are not happening per se. It has been postulated that there is a specific dose-response relationship between PA and potential bodily adaptions, where duration, frequency, intensity and type of activity are important factors to consider (Miko et al., 2020). Therefore, in publication II and III, several different PA variables were considered as predictor variables for new onset of MetS and its different risk factors. Habitual, as well as sports-related PA at baseline, and change in sports-related PA during time under observation with regard to duration, frequency, intensity and type of activity were assessed to calculate the weekly time spent with PA (minutes and MET-hours). However, only the weekly amount of time spent with PA and not intensity levels of PA was taken into consideration, even though metabolic equivalent of each type of activity was considered. Therefore, future research may need to take into account quantity and quality of PA, such as type and intensity of PA over time, and preferably assessed across the lifespan. With regard to potential health benefits, PA engagement on the one hand, and stability of sports participation on the other hand appear to be important factors (i.e. Friedman et al., 2008; Mertens et al., 2017). Based on this findings, it can be hypothesized that maintaining or even increasing continuous engagement in sports-related PA across the lifespan may be most effective in order to achieve desirable health benefits with regard to cardiometabolic risk reduction.

In this thesis, only the association between PA variables and morbidity (i.e. new onset of MetS or risk factors of MetS) was considered. However, as indicated in the model on the associations between physical behavior, health-related fitness, and health status by Bouchard et al. (2012), physical fitness may moderate the influence of PA on MetS (Lopes & Rodrigues, 2021), but fitness was not considered as potential covariate in the statistical models. Furthermore, in addition to the influence of PA on risk factors of MetS, diet also plays an important role when it comes to the direct influence on metabolism and their underlying processes (Saklayen, 2018). However, the models were also not controlled for diet.

As indicated in the introduction section of this thesis, biology of MetS has several dimensions and pathways of development. MetS is a complex, long-term developing pathophysiologic status that originates from an imbalance of caloric intake and energy expenditure, but is also affected by individual's genetics, sedentary lifestyle, and others factors like quality of food intake (Saklayen, 2018). In this thesis, several favorable associations between PA and blood-lipids (i.e. HDL, TG) were found. With regard to WC, a 38 % reduced risk for elevated WC was observed only for starting PA from below 16.6 to more than 16.6 METh per week. No other association between PA and risk of incident elevated WC was observed. A reason for this lack of association may be that WC is more impacted by other factors, such as nutrition rather than sports-related PA. However studies showed, that dietary intake and PA had significant independent effects on WC (Choi et al., 2012; Koh-Banerjee et al., 2003; Macdonald et al., 2003), and that weight was influenced more by reduced energy expenditure rather than increased energy intake (Macdonald et al., 2003). Additionally, from a medical point of view, WC is a rather stable variable compared to BP or BG levels, which may vary across the day and adapt very fast (Millar-Craig et al., 1978). Nevertheless, in this analyses, favorable associations between PA and BG were only found for stable PA behavior from baseline to follow-up. In this case, a long-term stable PA behavior (i.e. from baseline to follow-up) can be considered as important factor to potentially avoid insulin intolerance and, as a consequence, MetS. However, no favorable association between PA and reduced risk of incident elevated BP was found. In contrast, a 49 % elevated risk was found for higher sports-related PA level (METh per week) at baseline, and a 68 % elevated risk for incident elevated BP was found quitting sports-related PA, compared to the least active group. Even higher thresholds to indicate hypertension did not result in a favorable association between PA and a potential risk reduction. From a sports scientific point of view, the type of exercise, rather than sports participation in general, may be a more relevant factor when it comes to associations between PA and potential risk reduction of incident hypertension (Bouchard et al., 1993).

5.1 PERSPECTIVE

Based on the aforementioned limitations, future studies should consider several issues, e.g.

(a) in addition to the potential influence of PA on risk factors of MetS, diet also plays an important role when it comes to the direct influence on metabolism and their underlying processes (Saklayen, 2018). Thus, future models should be additionally controlled or adjusted for diet,

(b) applying other statistical methods in addition to HR regressions (e.g. latent growth curve modeling; linear mixed-modeling) in order to compensate for the limitations and bias (e.g. setting PA behavior at study entry compared to the PA behavior at the latest study visit in order to indicate change in PA behavior; excluding all unhealthy participants at study entry),

(c) take into account quantity and quality of PA, such as type and intensity of PA over time, and preferably across the lifespan (from a sports scientific point of view: the type of exercise, rather than the sports participation in general may be the more relevant factor when it comes to associations between PA and potential risk reductions),

(d) results of a systematic review of cross-sectional and longitudinal studies indicated that objectively measured light-intensity PA was inversely associated with risk factors including WC, TG levels, insulin, and presence of metabolic syndrome (Amagasa et al., 2018). Thus, future longitudinal studies should include objective PA measurement (e.g. accelerometry) to reduce recall in addition to PA assessment based on self-report bias (Burchartz et al., 2020),

(e) it remains important to have longitudinal studies with long follow-up periods to detect onset of risk factors of MetS and MetS.

As a conjoint task of global actions plans, governmental and societal structures, the prevention of risk factors of MetS is important. Like other epidemics, prevention and control of MetS and its risk factors should be a primary aim for stakeholders. The exact diagnosis of MetS may be complicated as it requires invasive procedures, i.e. blood testing. However, by knowing the underlying pathophysiologic pathways of MetS, even an increase in abdominal WC which can be assessed non-invasively may be promoted as a first alert signal to the general public in the prevention of NCDs (Saklayen, 2018).

Furthermore, in addition to potential health benefits of PA, the economic burden and negative health impacts of physical inactivity are significant. Between 2020 and 2030, almost 500 million new cases of preventable NCDs will occur. If there is no positive change in the current prevalence of physical inactivity, globally, it is estimated that treatment costs will exceed more than US$ 300 billion or around US$ 27 billion annually (World Health Organization, 2022a). For high-income countries, 70 % of expense on treatment for illness and diseases may be resulting from physical inactivity (World Health Organization, 2022a). Additionally, current global PA guidelines recommend relatively high amounts of moderate-to vigorous PA in order to elicit health benefits. However, results from this thesis show that even promoting medium amounts of sports-related PA (i.e. ≥ 75 minutes per week) may be associated with health benefits as well, and a lower PA threshold may be more appealing to individuals who have been physically inactive for extended periods of time. Therefore, to conclude, global action plans and national prevention strategies should consider the favorable impact of PA, but also the negative impact of physical inactivity on population's health.

Health is not only referring to being bodily unimpaired. In this thesis, the focus was mainly on the physiological association between PA and (risk factors of) MetS. Beyond the impact on the body itself, PA also has an impact on psychological and social factors, and vice versa, as described by multiple models (e.g. in the bio-psycho-social model by Engel (1976)). Despite the currently existing evidence of the protective health benefits of PA on NCDs and metabolic risk factors, on population level, numbers of incident risk factors of MetS are increasing. Despite the presence of action plans and public health strategies, which are postulating those beneficial and protective associations, individuals seem to have problems implementing a *healthy* behavior or changing it to a more *healthier* one. This means that there might be an intention-behavior gap on the individual level. The sole knowledge about a *healthy* lifestyle, is not sufficient to change a behavior. There are various motives (e.g. health benefits, well-being, enjoyment, social interaction, and social support) and barriers (e.g. time restrictions, fatigue, lack of energy, financial restrictions, health-related restrictions, low motivation, and shortage of facilities) related to PA, which may impact a person's decision to participate in PA or not (Pedersen et al., 2021). Thus, changing an individual's behavior from physically inactive to being (regularly) active is a complex process (Bronfenbrenner, 1979; Sallis et al., 2006; Sallis et al., 2008); and, unfortunately, most individuals fail to change their PA behavior to being physically active on a regular basis due to the complexity of factors, even if their motivation is high (Scholz et al., 2008). Furthermore, motives and barriers vary for persons with different social backgrounds, age, and sex, amongst others. Additionally, type of sports activity (e.g. competitive or not), social factors related to PA (e.g. guided or not), or reachability of facilities and access to facilities are important variables, which should also be considered for specific PA promotion programs (Pedersen et al., 2021). Thus, future studies should consider psychological and social factors in the analyses as well. From a public health scientific point of view, those factors are as important as physiological factors, as it should always be a multifaceted effort to address people's needs and help them to be more physically active. Thus, future actions plans and intervention strategies should address those individual needs as well.

As stated in the introduction section (please also refer to Figure 1), the development of evidence-based public health strategies is one of the major aims of epidemiology. Epidemiological studies provide and report information about specific health issues to health-politicians and other stakeholders. It is the major task of public health strategies to claim specific goals, prevention and interventions strategies to the population. However, epidemiology often suffers from a 'yes- but' approach (Jenicek, 1997) and struggles with the theoretical construct of causality, as associations between cause and effect are not easy to be proven empirically. Even results from experimental trials (i.e. randomized controlled trials) which are regarded as the 'gold standard' but are rarely applicable in epidemiology for ethical reasons, require testing for potential bias and misinterpretation (Neumeyer-Gromen et al., 2006; Rothman & Greenland, 2005). Thus, they also cannot provide ultimate or overarching evidence with regard to a certain research question. However, results from observational studies such as cross-sectional or longitudinal studies also contribute to this, albeit not on the highest level of evidence compared to experimental trials (Neumeyer-Gromen et al., 2006). To support researchers with their decisions, there are specific Bradford Hill criteria/ viewpoints (i.e. strength of association, consistency, specificity, temporality, dose-response, plausibility, coherence, experiment, analogy) to assess and evaluate causal relationships in epidemiology (Hill, 2015; Shimonovich et al., 2021). Despite those criteria, scientists and medical professionals always need to consider and weight those uncertainty, and must make a 'yes or no' decision (Jenicek, 1997).

Nevertheless, in this thesis, standard and well-established statistical methods were applied. Indeed, HR-regression models are considered a *state of the art* statistical approach in epidemiological research, particularly when results are to be reported to stakeholders or should inform a public health discussion. It might be appealing, to use methods derived from others sciences (e.g. psychology, biology, sociology, etc. …). However, *easy-to-read* numbers (i.e. % risk reduction) as used in this thesis are helpful in translating research findings into public discussions and platforms.

Overall, based on the results of this thesis, it can be postulated, that…

- … being physically active only for habitual reasons (e.g. working in the household, walking or biking for transportation, as well as gardening) may not be suitable to gain favorable health outcome with regard to MetS.
- … it is never too late to start participating in PA in order to gain favorable health benefits with regard to MetS.
- … it is better to perform even small amounts of PA, than not being physically active at all.
- … maintaining a stable PA engagement over life-time is associated with decreased risk of developing new onset of MetS.

5.2 CONCLUSION

In conclusion, this thesis provides additional evidence of an association between sports-related PA and a decreased risk of incident MetS and risk factors of MetS, i.e., being physically active at baseline, as well as remaining physically active or even starting sports-related PA during follow-up were associated with a reduced risk of incident MetS or individual risk factors of MetS. Furthermore, aside from sports participation in minutes per week, PA expressed in METh per week also appears to be an important predictor variable for incident MetS. This data shows that PA should be carried out at a rather high level with a rather high metabolic equivalent in order to achieve favorable health outcomes, whereas habitual PA was not related to the risk of incident MetS or individual risk factors of MetS. In addition, however, results on the association between PA and risk of new onset of elevated BP remain weak, and more research is needed in this regard. The findings reported in this doctoral thesis have implications for PA promotion in middle-aged adults aimed at increasing metabolic health, and underline the importance of structured PA health promotion programs and public health strategies, even at community-based levels.

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Chapter 1 - General introduction

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CHAPTER 2 - PUBLICATION I

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CHAPTER 5 - GENERAL DISCUSSION

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