Physical activity, vascular health, and delayed mortality: Evidence from international population-based studies

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For my parents

Contents

List of Abbreviations

AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMD	cardiovascular/metabolic disease
CT	computed tomography
CVD	cardiovascular disease
DEGS	German Health Interview and Examination Survey for Adults ("Studie zur Gesundheit Erwachsener in Deutschland")
ECG	electrocardiography
GEFU	Health Status Questionnaire ("Gesundheits-Follow-up")
HDL	high-density lipoprotein
HR	hazard ratio
ICD	International Classification of Diseases
KORA	Cooperative Health Research in the Region of Augsburg
LDL	low-density lipoprotein
MET	metabolic equivalent
MI	myocardial infarction
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MOSPA	MONICA Optional Study of Physical Activity
MPO	myeloperoxidase
MRI	magnetic resonance imaging
NCD	non-communicable disease
OR	odds ratio
Ox-LDL	oxidized low-density lipoprotein
PASE	Physical Activity Scale for the Elderly
SD	standard deviation
WHO	World Health Organization

1. Summary

Regular physical activity plays a key role in maintaining health and general well-being throughout the course of one's entire life. Despite its health-enhancing effects, physical activity levels remain low in many countries of the world. According to the World Health Organization, physical inactivity causes 3.2 million deaths worldwide each year. Although the positive impact of regular physical activity on human health - especially in the prevention of cardiovascular disease and premature mortality - is strongly supported by previous research, many important issues remain unresolved. There is a lack of population-based data regarding the association of physical activity with oxidative stress (a risk factor for atherosclerosis), with subtypes of stroke, with multimorbidity and with cause-specific mortality. Furthermore, little is known about the separate effects of physical activity in different settings (at work, for transportation purposes, in the household, and during leisure time) on the prevention of chronic diseases and, therefore, further epidemiological analyses are warranted.

Considering the high public health relevance of an active lifestyle, the aim of the present dissertation is to investigate possible and hitherto largely unknown associations of domain-specific physical activity with vascular health and delayed mortality.

The present dissertation consists of four articles. In the first manuscript, the association between domain-specific physical activity and oxidative stress was examined. Higher levels of leisure time physical activity were inversely associated with serum levels of the enzyme myeloperoxidase, but not with oxidized low-density lipoproteins. In the second article, a positive effect of ideal physical activity levels on the reduction of overall stroke risk, ischemic stroke risk and nonlacunar stroke risk was observed. Men and African-Americans seemed to benefit more from enhanced physical activity than women and Caucasians, respectively. In the third paper, the possible relation between physical activity and multimorbidity (defined as two or more chronic diseases within the same individual) was investigated. Increased activity levels were associated with decreased odds of multimorbidity in men, but not in women. In the fourth study addressing the effects of domain-specific activity on cause-specific mortality, activities during leisure time, in the household, and at work emerged as the most important physical activity domains in the prevention of total, cardiovascular, and cancer mortality.

This thesis emphasizes the high importance of an active lifestyle for health promotion on different levels of vascular health outcomes (physiological processes, single disease, accumulation of multiple diseases) and mortality. In particular, engagements in activities in the houshold, at work, and most importantly during leisure time play a significant role in the prevention of certain subtypes of stroke and cause-specific mortality. Furthermore, the present results support the hypothesis that increased activity is inversely associated with oxidative stress and multimorbidity. Based on the large volume of scientific evidence regarding the beneficial effects of physical activity on human health, public health agencies and health authorities should take action and develop, improve or revise, existing physical activity guidelines. These documents should advocate the integration of regular exercise into daily routines in addition to enhanced engagements in leisure time activities, thereby significantly increasing physical activity levels in the population.

2. Zusammenfassung

Regelmäßige Bewegung leistet in jeder Lebensphase einen wichtigen Beitrag zur Erhaltung der Gesundheit sowie des allgemeinen Wohlbefindens. Trotz seines gesundheitsfördernden Potenzials wird diese Ressource nur unzureichend genutzt. Schätzungen der Weltgesundheitsorganisation zufolge ist körperliche Inaktivität weltweit für 3,2 Millionen Todesfälle im Jahr verantwortlich. Obgleich der positive Einfluss regelmäßiger körperlicher Aktivität auf die menschliche Gesundheit, allen voran in der Prävention von Herzkreislauf-Erkrankungen und vorzeitiger Mortalität, in einigen populationsbasierten Studien bewiesen werden konnte, bleiben viele wichtige Fragestellungen offen. Bislang größtenteils ungeklärt sind Fragen bezüglich der Assoziation körperlicher Aktivität mit oxidativem Stress (als Risikofaktor der Arteriosklerosenbildung), mit Subtypen des Schlaganfalls, mit Multimorbidität und ursachenspezifischer Mortalität. Wenig empirisch belegt ist zudem die Frage, in welchem körperlichen Aktivitätssetting (in der Arbeit, zu Fuß oder mit dem Fahrrad zurückgelegte Wege, im Haushalt, in der Freizeit) die größten positiven Effekte regelmäßiger Bewegung auf die Prävention chronischer Erkrankungen zu verzeichnen sind. Um diese Sachverhalte zu klären, bedarf es weiterer epidemiologischer Analysen in populationsbasierten Studien.

Anknüpfend an die hohe gesellschaftliche Relevanz eines aktiven Lebensstils soll das Ziel meiner kumulativen Dissertation die Untersuchung möglicher, bisher weitgehend unbekannter Assoziationen zwischen regelmäßiger körperlicher Aktivität und physiologischen Prozessen und deren Folgeerkrankungen auf vaskulärer Ebene, sowie der vorzeitigen Mortalität sein.

Die vorliegende Dissertation umfasst vier Fachartikel. In der ersten Publikation ging ich der Frage nach, ob und in welchen Aktivitätsbereichen eine inverse Assoziation mit oxidativem Stress zu beobachten ist. Hierbei gingen höhere Freizeitaktivitätslevel mit niedrigeren Serumkonzentrationen des Enzyms Myeloperoxidase einher, jedoch nicht mit niedrigeren Serumkonzentrationen des oxidierten Lipoproteins niederer Dichte. In der zweiten Veröffentlichung wurde ein positiver Effekt von idealer körperlicher Aktivität auf die Risikoreduktion des Gesamtschlaganfalls, des ischämischen Schlaganfalls und des nichtlakunären Schlaganfalls beobachtet. Das dritte Manuskript befasste sich mit der möglichen Assoziation zwischen körperlicher Aktivität und Multimorbidität, definiert als zwei oder mehr chronische Krankheiten in derselben Person. Erhöhte Aktivitätslevel waren mit geringeren Odds für Multimorbidität bei Männern assoziiert, jedoch nicht bei Frauen. In einer vierten Studie zu settingspezifischer Aktivität und ursachenspezifischer Mortalität kristallisierten sich die Aktivitäten in der Freizeit, im Haushalt, und in der Arbeit als bedeutsamste Bewegungsfaktoren in der Prävention der Gesamtmortalität, der kardiovaskulären Mortalität und der Krebsmortalität heraus.

Die Ergebnisse der Doktorarbeit unterstreichen den hohen gesundheitsförderlichen Stellenwert eines aktiven Lebensstils, sowohl auf physiologischer Ebene, als auch auf der Ebene von individuellen und komplexen Folgeerkrankungen, sowie der vorzeitigen Mortalität. Insbesondere die aktive Teilnahme an sportlichen Freizeitaktivitäten, aber auch an Aktivitäten im Haushalt und während der Arbeit spielt eine bedeutsame Rolle in der Prävention von bestimmten Subtypen des Schlaganfalls und der ursachenspezifischen Mortalität. Des Weiteren unterstützen die Ergebnisse die Hypothese, dass vermehrte Aktivität invers mit

oxidativem Stress und Multimorbidität assoziiert ist. Gesundheitsbehörden sollten daher verstärkt Handlungsstrategien erstellen beziehungsweise weiterentwickeln, sowie Kampagnen starten, die neben der Freizeitaktivität die Integration von regelmäßiger Bewegung in Alltagssituationen befürworten, um das Bewegungsniveau in der Bevölkerung maßgeblich zu steigern.

3. Introduction

> "Lack of activity destroys the good condition of every human being while movement and methodical physical exercise save it and preserve it." [Plato]

3.1 Physical activity epidemiology

Regular physical activity[1] plays a key role in maintaining health and general well-being throughout the course of one's entire life. Already over 2,000 years ago, ancient Greek physicians, such as Hippocrates and Galen, recognized the significance of sufficient exercise and prescribed exercise for the prevention of diseases [2]. Yet, it was only in the early 1950s that the pioneer of physical activity epidemiology, Jeremy N. Morris, applied quantitative analysis to show that exercise prevents the onset of coronary heart disease [3, 4]. Since then, abundant scientific evidence has clearly documented the many beneficial effects of physical activity on human health and lower mortality rates. Physical activity has been shown to decrease the risk of cardiovascular disease (CVD), diabetes mellitus, and certain cancer types, as well as prevent obesity, osteoporosis, falls, and improve quality of life and mental health [5, 6, 7].

Despite the knowledge of health-enhancing effects of physical activity, engagement in activities remains poor in many countries worldwide. The use of technological advancements, in particular, is leading populations to a more sedentary lifestyle [8]. According to the World Health Organization (WHO), 3.2 million deaths annually are attributable to a lack of physical activity [9]. The importance of physical inactivity as a health risk factor led to a series of physical activity articles recently published in the *Lancet*, which included the investigation of global physical activity levels among adults from 122 countries, as well as the negative effects of inactivity on non-communicable diseases (NCD) [10, 11]. Hallal and co-workers reported alarmingly high numbers of global inactivity levels: 31.1% (95% confidence interval [CI]: 30.9-31.2) of individuals aged 15 and older did not reach the recommended[2] physical activity levels [10].

Among the German population, physical activity levels have clearly risen since the last nationwide survey in 1998, according to the first results of the nationwide "German Health Interview and Examination Survey for Adults (DEGS)" examining 7,988 participants aged 18-79 years. Nonethless, only 25.4% of men and 15.5% of women reached WHO's recommended minimum activity level of 2.5 hours per week [12].

A serious repercussion of these developments is the continuously rising global prevalence of NCDs, which are now the leading cause of morbidity and mortality worldwide.

[1] The general term "physical activity" includes exercise, physical fitness, sports and health sports. Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [1, p. 126]

[2] Individuals were categorized as physically inactive if they did not meet any of the following criteria, based on the 2008 Physical Activity Guidelines for Americans: "(1) 30 min of moderate-intensity physical activity on at least 5 days per week, (2) 20 min of vigorous-intensity physical activity on at least 3 days per week, (3) an equivalent combination achieving 600 metabolic equivalent (MET)-min per week" [10, p. 2]. One MET is defined as the energy spent sitting quietly (corresponds to 1 $kcal \cdot kg^{-1} \cdot h^{-1}$).

The urgent need for action prompted the United Nations to hold a high level meeting in September 2011, in order to set up an international agenda for the prevention and control of the major NCDs: heart disease, stroke, cancer, diabetes, and chronic respiratory diseases [13]. The *Lancet* NCD Action Group and the NCD Alliance identified physical activity as one of five prevention strategies to counter the negative trend of rising NCDs [14], underscoring the importance of the need to increase activity levels globally.

3.2 Current state of research

Over the course of several decades, substantial empirical evidence from large population-based studies has been accumulated regarding the overall benefits of regular physical activity [5, 6, 7]. Although the impact of physical activity on human health, especially in CVD research, has been studied extensively, many issues remain unexplored to date. In particular, there are research gaps in the field of large population-based epidemiological studies on the association of physical activity with certain vascular outcomes, such as oxidative stress or stroke subtypes. In addition, there is a shortage of data regarding the association of separate domain-specific physical activity (work, transportation, household, leisure time) with chronic diseases and premature death. For persons unable to participate in leisure time physical activity, information on the preventive aspect of non-exercise activities, such as household or work activities, is crucial.

Linkage of selected topics

In the present dissertation, the potential linkage of physical activity and health-related topics is analyzed on several levels, ranging from physiological processes, over single disease and multiple diseases to mortality. Figure 1 outlines the hypothesized relationship of physical activity as an exposure variable and the selected topics, which serve as a basis for the manuscripts comprising this dissertation.

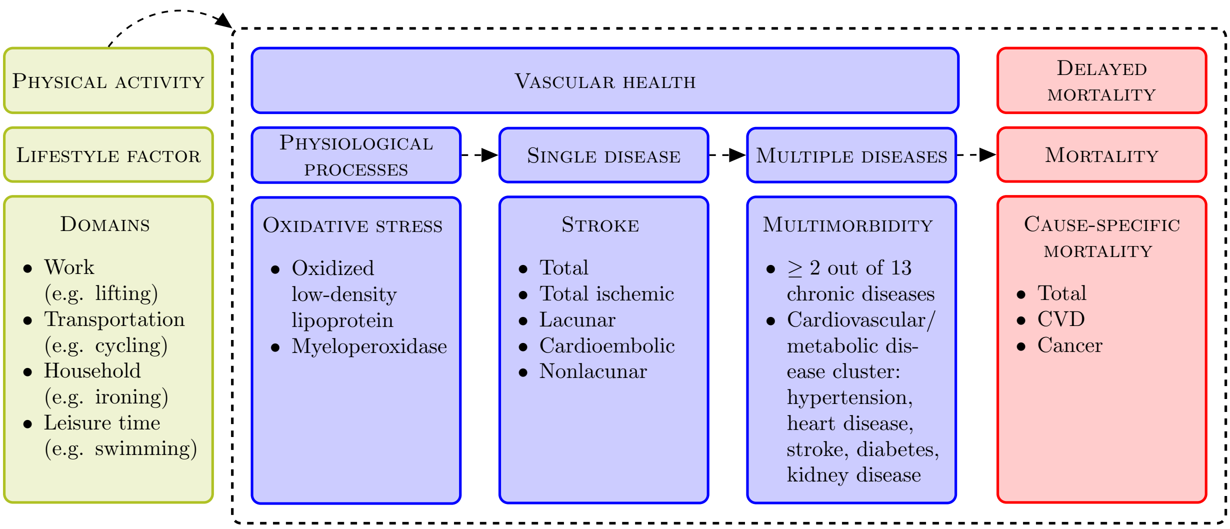

Figure 1: Linkage between the selected topics and physical activity.

Physical activity and oxidative stress

The first level considers physical activity and physiological processes. From the relevant literature it becomes apparent that oxidative stress is associated with several chronic diseases, such as atherosclerosis and CVD [15, 16]. Bouts of exercise are thought to reduce levels of oxidative stress in the blood through a stronger stimulation of antioxidants [17]. Previous work in this context is limited to the impact of exercise-induced effects in intervention studies of small sample sizes [18]. Therefore, the potential association between regular physical activity and oxidative stress has not been given sufficient attention up to now. One of the very few larger studies that used regular leisure time physical activity - instead of exercise-induced training effects - as an independent variable reported an association between physical activity and selected oxidative stress markers (especially lipid-peroxides) among 488 female participants [19]. Additional large epidemiological studies that provide sex-specific and domain-specific physical activity data within a comprehensive sample size are warranted. Furthermore, no study has specifically investigated the relation between physical activity and the enzyme myeloperoxidase (MPO) which serves as a catalyst for the formation of tissue-damaging oxidized low-density lipoproteins (ox-LDL) [16].

Physical activity and stroke

The second level deals with physical activity and an individual disease example, namely stroke. Physical inactivity was named as one of the modifiable stroke risk factors in the 2011 American Heart Association's (AHA) and American Stroke Association's Primary Prevention of Stroke Guidelines, along with hypertension, diabetes, obesity, smoking, and others [20]. Previous studies examining the potential beneficial effects of physical activity on stroke risk have yielded conflicting results. Even though a large body of literature generally found evidence for the preventive value of physical activity [21, 22, 23], other studies failed to concur [24, 25]. Certain other stroke risk factors such as diabetes, current smoking, and waist-to-hip ratio were shown to vary by ischemic stroke subtype (lacunar, cardioembolic, nonlacunar) in the Atherosclerosis Risk in Communities (ARIC) Study [26]. Consequently, investigating the effects of physical activity on stroke subtypes may refine our understanding of its potential preventive health effect on stroke risk and is therefore an important research gap that needs to be addressed.

Physical activity and multimorbidity

The co-occurrence of two or more chronic diseases in one person, commonly defined as multimorbidity, has increased dramatically over the past decades, in part due to rising life expectancies in most countries of the world [27]. Although physical activity has been established as a key health-enhancing factor in the prevention of many chronic diseases, epidemiological studies addressing the association between physical activity and multimorbidity are lacking, and the two major studies on this topic yielded mixed results. While Kaplan et al. reported that being more frequently active was related to the absence of chronic diseases among 12,611 people aged 65 and older [28], Hudon et al. concluded from their results that physical activity was not related to multimorbidity among 16,782 adults aged 18-69 years [29]. Hence, further studies need to clarify this potential association, additionally providing more detailed information, such as sex-specific differences, domain-specific physical activity effects, and a more detailed physical activity measure, taking into account both frequency and intensity of physical activity.

Physical activity and mortality

The effects of regular physical activity on mortality have been extensively investigated in many epidemiological cohort studies over the past several years, suggesting a protective effect from enhanced physical activity on premature mortality [30, 31, 32, 33]. The majority of the epidemiological studies have mainly focused on the effects of a single domain of physical activity, predominantly on work or leisure time physical activity. However, it is essential to also include other settings, such as household or transportation physical activity. Few studies have focused on domain-specific activities performed in everyday life [30, 32, 33] in association with mortality, and only one study has specifically analyzed the four most common domains together, namely physical activity at work, for transportation purposes (cycling/walking), in the household, and during leisure time [34]. Furthermore, there is also a shortage of population-based studies that investigate different types and intensities of physical activity in association with cause-specific mortality, particularly cancer mortality.

Thus, considering the current state of research, the four selected health topics can be divided into the following categories:

- Newly established research areas (physical activity and oxidative stress)
- Poorly researched complex areas (physical activity and stroke subtypes, physical activity and multimorbidity)
- New focus in fairly well-researched areas (domains of physical activity and mortality)

3.3 Specific aims and brief overview of methods

Based on the above-outlined research gaps, the aim of this cumulative dissertation is to investigate the health significance of regular physical activity, performed in different domains, in large epidemiological population-based studies from Germany and the United States. More specifically, the main focus of the present thesis is to elucidate the association between domain-specific physical activity and oxidative stress, stroke subtypes, multimorbidity, and mortality among middle-aged and elderly individuals. Consequently, four specific research questions are addressed in this dissertation:

1. Are higher levels of physical activity associated with a reduced concentration of serum oxidative stress markers MPO and ox-LDL?
2. Do the assumed beneficial effects of physical activity on stroke vary by ischemic stroke subtypes?
3. Is physical activity inversely associated with multimorbidity among the elderly?
4. Which of the four physical activity domains shows the strongest association between increased exercise and reduced risk of all-cause, CVD, and cancer mortality?

The present doctoral thesis is based on four manuscripts, all of which are published in internationally peer-reviewed journals. For all papers, I am the first author and was significantly involved in developing the research questions. Furthermore, I performed the statistical analyses and interpreted the results together with my supervisors. I have also written all parts of the manuscript drafts, created the tables and figures, incorporated the co-authors' comments and finalized the manuscript based on reviewers' comments from each respective journal.

Study populations

For the present dissertation, data were derived from two well-known epidemiological studies: the MONICA/KORA Augsburg Studies (Monitoring of Trends and Determinants in Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg) and the ARIC Study (Atherosclerosis Risk in Communities).

The MONICA/KORA Augsburg Studies were initiated in the early 1980s as part of WHO's large multinational epidemiological MONICA Study to analyze global population trends of heart disease, stroke and their associated risk factors in 21 countries over a period of 10 years [35]. Data were collected via face-to-face interviews and examinations at four different points in time: Study 1 (S1, 1984/85, n=4,022, age: 25-64 years), Study 2 (S2, 1989/90, n=4,940, age: 25-74 years), Study 3 (S3, 1994/95, n=4,856, age: 25-74 years), Study S4 (S4, 1999-2001, n=4,261, age: 25-74 years). In addition, three health surveys ("Gesundheits-Follow-up") were implemented via postal questionnaires to ascertain the current health status of the MONICA/KORA participants (GEFU 1: 1997/1998, GEFU 2: 2002/2003, GEFU3: 2008/2009) [36, 37]. In 2008/2009, the KORA-Age Study (n=1,079) was completed, which is a follow-up of all S1-S4 participants born in 1943 or earlier.

The ARIC Study is a large prospective population-based cohort study of 15,792 men and women aged 45-64 years at baseline in 1987-1989 [38]. Its objective is to examine the etiology of atherosclerosis, clinical atherosclerotic diseases, and CVD risk factors. Individuals were selected from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. The first exam was completed in 1987-89, the second in 1990-92, the third in 1993-95, the fourth in 1996-98, and the fifth in 2010-2012. Annual follow-up by telephone ensures continued contact with ARIC participants and is applied to assess the health status of the cohort.

Assessment of physical activity

In all MONICA/KORA Studies S1-S4, a basic physical activity module comprised of four items[3] was used to categorize the self-reported activity level of the participants into the preformed categories: no, low, moderate and high. Additionally, in S2, the detailed MOSPA questionnaire (MONICA Optional Study of Physical Activity), developed by WHO and validated in previous studies [39, 40], was applied to quantify individual physical ac-

[3] Participants were asked to indicate (1) the weekly hours engaged in physical activity in the summertime, (2) the weekly hours engaged in physical activity in the wintertime, (3) the intensity of physical activity at the current occupation, and (4) the daily amount of minutes spent walking.

tivity levels in four different settings[4]. Through the participants' indication of the time and intensity spent on domain-specific activities, a standardized program based on the Compendium of Physical Activities [41] and provided by the Centers for Disease Control and Prevention (CDC) allowed the calculation of METs. Based on the calculated energy expenditure expressed in METs, individuals were categorized into no, light, moderate, and vigorous physical activity. In the KORA-Age Study, the detailed PASE (Physical Activity Scale for the Elderly) was used to determine self-reported, domain-specific continuous activity scores [42]. In the ARIC study, the Baecke questionnaire [43], along with the updated Compendium of Physical Activities [44], served as basis for the calculation of minutes per week of exercise, which were then classified corresponding to the AHA ideal CVD health guidelines for adults aged 20 years and above as poor, intermediate, and ideal physical activity [45].

Ascertainment of outcome variables

Oxidative stress markers: Nonfasting blood samples were retrieved from individuals under standardized conditions. Until analysis, serum samples were stored at −80 °C. Serum levels of ox-LDL and MPO were measured by Enzyme-linked Immunosorbent Assays.

Stroke and its subtypes: Evidence of hospitalized stroke events were ascertained from physician review, and stroke subtypes were classified using neuroimaging results.

Multimorbidity: Multimorbidity was defined as the presence of two or more chronic diseases out of a list of thirteen chronic conditions. The cardiovascular/metabolic disease (CMD) cluster consisted of five diseases (see Figure 1) and CMD multimorbidity was also defined as two or more chronic diseases within one individual. This information was collected through a postal self-administered questionnaire and a standardized telephone interview.

Mortality: Death certificates from local authorities were used to code the cause of death according to the 9th revision of the International Classification of Diseases.

Statistical analyses

For the two cross-sectional analyses, multivariable linear and logistic regression models were applied for analytic studies of associations between physical activity and oxidative stress and multimorbidity, respectively. For both longitudinal analyses (with the health outcomes of stroke subtypes or mortality), Cox proportional hazards models were calculated. All analyses were adjusted for relevant confounding factors and were completed using SAS version 9.2 (SAS Institute, Cary, NC). Tests were considered statistically significant with a two-sided $P < 0.05$.

[4]Equivalent to the above-mentioned domains: work, transportation, household, and leisure time physical activity.

3.4 Results

In the first manuscript, the association between domain-specific physical activity and the oxidative stress markers ox-LDL and MPO was investigated among 1,820 persons aged 35-74 who participated in one of the three MONICA/KORA Augsburg Studies (S1, S2, S3) and had available blood samples. Participants engaged in high leisure time physical activity levels had significantly lower MPO concentrations (124.2 $\mu g/ml$, 95% CI: 116.8-132.0) in the circulating blood as compared to the inactive group (133.5 $\mu g/ml$, 95% CI: 127.6-139.6). For the two other physical activity domains "work" and "walking", no statistically significant inverse association with MPO levels could be observed. With regard to the second biomarker, no physical activity domain was related to ox-LDL ($P_{trend} > 0.05$).

The second publication represents a longitudinal study in which ARIC data from 13,069 individuals aged 45-64 years were used to examine the impact of physical activity on stroke risk. 648 total incident ischemic strokes occurred during a median-follow-up of 18.8 years. Among the three ischemic subtypes, nonlacunar stroke was the most common subtype (n=354), followed by cardioembolic (n=150) and lacunar (n=144) stroke. Significant risk reductions for total stroke (ischemic and hemorrhagic strokes, n=740), total ischemic stroke and nonlacunar stroke were found with higher levels of physical activity. The hazard ratios (HR) for participants in the ideal physical activity group were significantly lower as compared to the poor activity group, which served as the reference. HRs (95% CI) were 0.78 (0.62-0.97) for total stroke, 0.76 (0.59-0.96) for total ischemic stroke and 0.71 (0.51-0.99) for nonlacunar stroke. In addition, sex- and race-specific analyses were conducted and the results revealed that the inverse association between physical activity and stroke seemed to be more pronounced in men compared to women, as well as in African-Americans compared to Caucasians.

The aim of my third research topic was to clarify whether physical activity was inversely related to multimorbidity among 1,007 elderly men and women aged 65 and older who participated in the 2008/2009 KORA-Age Augsburg Study. The prevalence of multimorbidity was slightly higher in women (68.5%) than in men (62.3%). Of the thirteen chronic conditions[5], hypertension (62.3%) was the most frequently reported, followed by eye disease (45.3%). Multivariable adjusted odds ratios (OR) of multimorbidity were lower with increasing physical activity levels among men, but not among women. ORs and 95% CI for an increase in the PASE total score by one standard deviation were 0.73 (0.60-0.90) for men, and 1.05 (0.83-1.33) for women. Among men, CMD multimorbidity was associated with both the PASE total score (OR: 0.69, 95% CI: 0.56-0.86) and the PASE household score (OR: 0.76, 95% CI: 0.63-0.93). After dividing the continuous PASE total score into quartiles, it became apparent that the observed inverse association among men was exclusively observed in the highest versus the lowest quartile of physical activity.

The main objective of my fourth manuscript was to elucidate which physical activity domain was most efficient in reducing all-cause, CVD or cancer mortality among 4,672 persons aged 25-74 years who participated in the second MONICA/KORA Augsburg Study (S2). After a median-follow-up of 17.8 years, a total of 995 deaths occurred, of which 452 were CVD-related and 326 were cancer-related. Across all physical activity domains, leisure

[5] Heart disease, kidney disease, joint disease, lung disease, gastrointestinal disease, neurologic disease, liver disease, eye disease, depression/anxiety, hypertension, stroke, diabetes mellitus, cancer.

time proved to be most effective in reducing mortality risk. The HRs (95% CI) for vigorous versus no leisure time physical activity were 0.48 (0.36-0.65) for all-cause mortality, 0.50 (0.31-0.79) for CVD mortality and 0.36 (0.23-0.59) for cancer mortality. In addition, light household activity showed significant risk reductions for both all-cause mortality (HR 0.82, 95% CI: 0.71-0.95) and CVD mortality (HR 0.72, 95% CI: 0.58-0.89). HRs (95% CI) for moderate versus light work activity were 0.69 (0.48-1.00) for all-cause mortality and 0.54 (0.31-0.93) for CVD mortality. Transportation physical activity, however, did not seem to have a protective effect against premature mortality.

3.5 Conclusions and future directions

This work confirms the positive effects of regular physical activity on selected health outcomes and extends previous findings in the field of physical activity epidemiology by thoroughly investigating the role of domain-specific physical activity.

Specifically, leisure time physical activity seems to counteract increased oxidative stress levels in the blood and the occurrence of multimorbidity among men; however, due to the cross-sectional design of these two studies, interpretation has to be made with caution, since the temporality of effects cannot be identified. In addition, leisure time physical activity appears to prevent stroke onset, while leisure time, household and work physical activity seem to decrease the risk of cause-specific mortality. The hypothesized preventive nature of transportation physical activity, on the contrary, could not be proven.

Despite the number of strengths of the MONICA/KORA and ARIC Studies, such as the population-based design and large sample sizes, as well as the careful and standardized evaluation of risk factors in each respective study, it needs to be noted that physical activity measurements were always based on self-report and therefore prone to reporting bias. Thus, further research with objectively measured physical activity levels in large epidemiological studies is needed to verify these results. In addition, the observed associations between physical activity and both oxidative stress and multimorbidity need to be verified in longitudinal studies. Future studies might also be directed at the investigation of dose-response relationships of physical activity with the presented health outcomes, and at possible negative effects of physical activity among aged populations.

Overall, this thesis highly advocates the engagement in exercise (leisure time) activities for enhancing human health. Although some beneficial effects of non-exercise (work and household) activities were observed when disentangling the health effects of the different domains of physical activity, the highest effects were found for leisure time activities such as swimming or jogging. These results underpin the high public health importance of an active lifestyle and additionally encourage the engagement in activities performed in daily routines. Unfortunately, physical activity as a prevention and intervention strategy is still heavily neglected. Therefore, public health agencies and health authorities should be strenghtened in their efforts to develop and endorse adequate guidelines and campaigns to increase activity levels in the population. In view of global population aging and the NCD burden that is associated with growing life expectancies around the world, it is imperative to use physical activity as an important dimension of prevention.

3.6 Bibliography

[1] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–131.

[2] Berryman JW. The tradition of the "six things non-natural": exercise and medicine from Hippocrates through ante-bellum America. Exerc Sport Sci Rev. 1989;17:515–559.

[3] Blair SN, Davey Smith G, Lee IM, Fox K, Hillsdon M, McKeown RE, et al. A tribute to Professor Jeremiah Morris: the man who invented the field of physical activity epidemiology. Ann Epidemiol. 2010;20(9):651–60.

[4] Paffenbarger R Jr, Blair SN, Lee IM. A history of physical activity, cardiovascular health and longevity: the scientific contributions of Jeremy N Morris, DSc, DPH, FRCP. Int J Epidemiol. 2001;30(5):1184–1192.

[5] Haskell WL, Blair SN, Hill JO. Physical activity: health outcomes and importance for public health policy. Prev Med. 2009;49(4):280–282. Available from: http://dx.doi.org/10.1016/j.ypmed.2009.05.002.

[6] Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report, 2008. U.S.Department of Health and Human Services; 2008.

[7] World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010.

[8] Cavill N, Kahlmeier S, Racioppi F. Physical activity and health in Europe: evidence for action. Copenhagen: WHO Regional Office for Europe; 2006.

[9] World Health Organization. Physical activity. World Health Organization; 2012. [cited 12 August 2012]. Available from: http://www.who.int/topics/physical_activity/en/.

[10] Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380(9838):247–257. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60646-1.

[11] Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219–229. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61031-9.

[12] Kurt BM. Erste Ergebnisse aus der "Studie zur Gesundheit Erwachsener in Deutschland" (DEGS). Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2012;55(8):980–990. Available from: http://dx.doi.org/10.1007/s00103-012-1504-5.

[13] Beaglehole R, Bonita R, Alleyne G, Horton R, Li L, Lincoln P, et al. UN High-Level Meeting on Non-Communicable Diseases: addressing four questions. Lancet. 2011;378(9789):449–455.

[14] Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, et al. Priority actions for the non-communicable disease crisis. Lancet. 2011;377(9775):1438–1447.

[15] Holvoet P, Jenny NS, Schreiner PJ, Tracy RP, Jacobs DR, MESoA. The relationship between oxidized LDL and other cardiovascular risk factors and subclinical CVD in different ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2007;194(1):245–252.

[16] Strobel NA, Fassett RG, Marsh SA, Coombes JS. Oxidative stress biomarkers as predictors of cardiovascular disease. Int J Cardiol. 2011;147(2):191–201. Available from: `http://dx.doi.org/10.1016/j.ijcard.2010.08.008`.

[17] Aldred S. Oxidative and nitrative changes seen in lipoproteins following exercise. Atherosclerosis. 2007;192(1):1–8. Available from: `http://dx.doi.org/10.1016/j.atherosclerosis.2007.02.001`.

[18] Elosua R, Molina L, Fito M, Arquer A, Sanchez-Quesada JL, Covas MI, et al. Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. Atherosclerosis. 2003;167(2):327–334.

[19] Covas MI, Elosua R, Fit M, Alcántara M, Coca L, Marrugat J. Relationship between physical activity and oxidative stress biomarkers in women. Med Sci Sports Exerc. 2002;34(5):814–819.

[20] Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(2):517–584.

[21] Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. Stroke. 2003;34(10):2475–2481. Available from: `http://dx.doi.org/10.1161/01.STR.0000091843.02517.9D`.

[22] Oguma Y, Shinoda-Tagawa T. Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. Am J Prev Med. 2004;26(5):407–418. Available from: `http://dx.doi.org/10.1016/j.amepre.2004.02.007`.

[23] Wendel-Vos GCW, Schuit AJ, Feskens EJM, Boshuizen HC, Verschuren WMM, Saris WHM, et al. Physical activity and stroke. A meta-analysis of observational data. Int J Epidemiol. 2004;33(4):787–798. Available from: `http://dx.doi.org/10.1093/ije/dyh168`.

[24] Evenson KR, Rosamond WD, Cai J, Toole JF, Hutchinson RG, Shahar E, et al. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study. Stroke. 1999;30(7):1333–1339.

[25] Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H. A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. Stroke. 1997;28(1):45–52.

[26] Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke. 2006;37(10):2493–2498. Available from: http://dx.doi.org/10.1161/01.STR.0000239694.19359.88.

[27] Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev. 2011;10(4):430–439. Available from: http://dx.doi.org/10.1016/j.arr.2011.03.003.

[28] Kaplan MS, Newsom JT, McFarland BH, Lu L. Demographic and psychosocial correlates of physical activity in late life. Am J Prev Med. 2001;21(4):306–312.

[29] Hudon C, Soubhi H, Fortin M. Relationship between multimorbidity and physical activity: secondary analysis from the Quebec health survey. BMC Public Health. 2008;8:304. Available from: http://dx.doi.org/10.1186/1471-2458-8-304.

[30] Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. Arch Intern Med. 2000;160(11):1621–1628.

[31] Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239–246. Available from: http://dx.doi.org/10.1097/HJR.0b013e3282f55e09.

[32] Barengo NC, Hu G, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. Eur Heart J. 2004;25(24):2204–2211. Available from: http://dx.doi.org/10.1016/j.ehj.2004.10.009.

[33] Matthews CE, Jurj AL, Shu XO, Li HL, Yang G, Li Q, et al. Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. Am J Epidemiol. 2007;165(12):1343–1350. Available from: http://dx.doi.org/10.1093/aje/kwm088.

[34] Besson H, Ekelund U, Brage S, Luben R, Bingham S, Khaw KT, et al. Relationship between subdomains of total physical activity and mortality. Med Sci Sports Exerc. 2008;40(11):1909–1915. Available from: http://dx.doi.org/10.1249/MSS.0b013e318180bcad.

[35] Tunstall-Pedoe H, Kuulasmaa K, Tolonen H, Davidson M, Mendis S, Project WM. MONICA monograph and multimedia sourcebook: world's largest study of heart disease, stroke, risk factors, and population trends 1979-2002. Geneva: World Health Organization; 2003.

[36] Holle R, Happich M, Löwel H, Wichmann HE. KORA–a research platform for population based health research. Gesundheitswesen. 2005;67 Suppl 1:S19–S25.

[37] Löwel H, Döring A, Schneider A, Heier M, Thorand B, Meisinger C. The MONICA Augsburg surveys–basis for prospective cohort studies. Gesundheitswesen. 2005;67 Suppl(S13-8).

[38] The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129(4):687–702.

[39] Iqbal R, Rafique G, Badruddin S, Qureshi R, Gray-Donald K. Validating MOSPA questionnaire for measuring physical activity in Pakistani women. Nutr J. 2006;5:18. Available from: `http://dx.doi.org/10.1186/1475-2891-5-18`.

[40] Roeykens J, Rogers R, Meeusen R, Magnus L, Borms J, de Meirleir K. Validity and reliability in a Flemish population of the WHO-MONICA Optional Study of Physical Activity Questionnaire. Med Sci Sports Exerc. 1998;30(7):1071–5.

[41] Ainsworth BE, Haskell WL, Leon AS, Jacobs D Jr, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993;25(1):71–80.

[42] Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. 1993;46(2):153–162.

[43] Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;36(5):936–942.

[44] Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 Suppl):S498–S504.

[45] Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121(4):586–613.

4. Publications

4.1 Myeloperoxidase, but not oxidized LDL is associated with leisure-time physical activity: Results from the MONICA/KORA Augsburg Studies 1984 – 1995

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Myeloperoxidase, but not oxidized LDL, is associated with leisure-time physical activity: Results from the MONICA/KORA Augsburg Studies 1984–1995

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ABSTRACT

Objective: Oxidative stress-induced cell damage contributes to several chronic conditions such as cardiovascular disease, but only very few population-based studies have examined the influence of regular physical activity (PA) on oxidative stress.

Methods: 1820 men and women aged 35–74 years were randomly drawn from three population-based MONICA/KORA Augsburg Studies conducted between 1984 and 1995. Geometric means of the oxidative stress markers myeloperoxidase (MPO) and oxidized LDL (ox-LDL) were calculated and multiple linear regression was performed to assess their associations with three self-reported PA domains, namely work, leisure-time or walking.

Results: Mean MPO concentrations were lower for participants engaged in high leisure-time PA (124.2 μg/ml; 95%-CI, 116.8–132.0) compared to the inactive reference group (133.5 μg/ml; 95%-CI, 127.6–139.6) (P_{trend} across PA levels: 0.007). No significant association between ox-LDL and PA domains was observed (P_{trend} between 0.162 and 0.803).

Conclusion: These data indicate that regular leisure-time PA may reduce MPO concentrations.

1. Introduction

Oxidative stress has been linked to many chronic diseases, including atherosclerosis and its sequelae, cardiovascular disease (CVD) [1–3]. Oxidized low-density lipoprotein (ox-LDL) in particular has been suggested to play a key role in the manifestation of atherosclerosis by building foamy macrophages, a massive cellular accumulation of cholesterol, which results in fatty streaks in the endothelium [4]. The enzyme myeloperoxidase (MPO) is abundant in neutrophils and through its production of oxidizing agents contributes to the peroxidation of LDL and further pathologies of CVD [3,5].

During excessive exercise, contracting myocytes produce reactive oxygen and nitrogen species that may lead to cell damage if plasma and cellular antioxidant levels are insufficient. Long-term moderate physical activity, however, may reduce oxidative stress through increased stimulation of antioxidants [6,7].

For the most part, research has focused on the acute state of exercise-induced oxidative stress [8] or the effect of several week-long exercise intervention programs on oxidative stress levels [9,10], and studies have mainly been conducted in rather small samples. Epidemiological data from large population-based studies regarding domain-specific physical activity (work, transportation, household, leisure-time), however, are lacking. Furthermore, MPO has not been given sufficient attention in this context.

The aim of the present study was to elucidate the relationship between physical activity performed in daily routines and two markers of oxidative stress related to CVD among 1820 middle-aged men and women.

2. Research design and methods

The presented data are based on three independent cross-sectional MONICA/KORA Augsburg Studies (S1, S2, S3) conducted between 1984 and 1995. Details on the design and sampling frame have been described elsewhere [11]. The final population for the current analysis included 1820 individuals aged 35–74 years with complete data from a random sample subset of participants with biomarker measurements stratified by sex and survey ($n = 2225$). Persons with missing values on oxidative stress markers

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Table 1
Adjusted geometric means[a] (95% CI) of ox-LDL and MPO according to domain and physical activity level.

	No	Low	Moderate	High	P_{trend}
Leisure-time	$n = 857$	$n = 269$	$n = 431$	$n = 263$	
Ox-LDL (U/ml)	87.3 (85.2–89.5)	88.5 (85.6–91.4)	87.7 (85.1–90.3)	86.6 (83.7–89.7)	0.803
MPO (μg/ml)	133.5 (127.6–139.6)	127.6 (120.3–135.3)	126.6 (120.4–133.2)	124.2 (116.8–132.0)	0.007
	No	Light	Moderate	Heavy	P_{trend}
Work	$n = 401$	$n = 581$	$n = 680$	$n = 158$	
Ox-LDL (U/ml)	88.3 (85.8–90.9)	87.5 (85.3–89.9)	86.3 (83.9–88.8)	88.0 (84.6–91.4)	0.296
MPO (μg/ml)	128.0 (121.7–134.6)	130.5 (124.3–137.1)	130.0 (124.0–136.3)	130.7 (120.8–141.5)	0.602
	<15 min/day	15–30 min/day	30–60 min/day	>60 min/day	P_{trend}
Walking	$n = 319$	$n = 282$	$n = 520$	$n = 699$	
Ox-LDL (U/ml)	86.4 (83.7–89.1)	86.5 (83.7–89.3)	88.2 (85.9–90.5)	87.9 (85.6–90.4)	0.162
MPO (μg/ml)	132.9 (125.2–141.1)	130.4 (122.8–138.5)	125.3 (119.6–131.4)	131.4 (125.4–137.6)	0.675

[a] Adjusted for age, sex, survey, education, body mass index, alcohol consumption, smoking status, actual hypertension, diabetes, total-to-HDL cholesterol ratio, dietary habits, and self-reported limited PA due to health problems.

($n = 318$), physical activity ($n = 7$) or any of the covariables ($n = 11$) were excluded as well as subjects taking statins, anticoagulants or antiplatelet drugs ($n = 69$).

Self-reported physical activity levels were measured through interview items that assessed the time per week spent on walking, work, and leisure-time physical activity. The following four categories were specified for leisure-time activity during summer and winter time: 0 (no), <1 (low), 1–2 (moderate), and >2 h/week (high). Work activity was classified into no, light, moderate, and heavy physical work. The average amount of time spent on walking per day was categorized into <15 min, 15–30 min, 30–60 min, and >60 min. In S2, the detailed MONICA Optional Study on Physical Activity (MOSPA) questionnaire was used to more precisely define physical activity domains. Based on the individual's response on the weekly time and intensity usually spent on work, transportation (walking/biking), household, and leisure-time physical activity, metabolic equivalents (METs) were calculated and participants were classified into no, light (<3.0 METs), moderate (3.0–6.0 METs), and vigorous physical activity (>6.0 METs), as described elsewhere [12].

Nonfasting blood samples were collected from all participants under standardized conditions [13] and were stored at −80 °C until analysis. Serum levels of ox-LDL and MPO were both measured by ELISAs from Mercodia, Uppsala, Sweden. The intra- and inter-assay coefficients of variation were <10.0%.

Detailed information on the assessment and definition of the covariables education, body mass index, alcohol consumption, smoking status, actual hypertension, diabetes, total-to-HDL cholesterol ratio, dietary habits, and self-reported limited physical activity due to health problems as well as further information on physical activity variables are shown in the supplementary methods.

3. Statistical analyses

Ox-LDL and MPO were log-transformed because of a skewed distribution. Means (S.D.) and relative frequencies were used to describe the study population according to physical activity levels. Differences across the groups were tested with analysis of variance and a χ^2 test. Multivariable linear regression was applied to examine the association between physical activity and ox-LDL or MPO, in models adjusted for the above-mentioned variables. Data (S1, S2, S3) were weighted to account for the sampling by using sex- and survey-specific ratios of the source and the final population. A corresponding P value for linear trend was calculated by treating exercise categories as ordinal variables. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

4. Results

14.4% of the study population reported no, 23.7% low activity, 14.8% moderate, and 47.1% high leisure physical activity. Two thirds of the individuals in the highest activity category were men. Subjects who were moderately and highly physically active had a higher education and were less prone to diabetes, hypertension or adverse health behavior such as smoking or excessive alcohol consumption ($p < 0.05$) (Supplementary Table 1).

As shown in Table 1, analyses demonstrate that MPO concentrations were significantly lower in participants who engaged in higher levels of leisure-time physical activity ($P_{trend} = 0.007$). The greatest differences in MPO concentrations are depicted between the inactive (133.5 μg/ml; 95%-CI, 127.6–139.6) and the low activity group (127.6 μg/ml; 95%-CI, 120.3–135.3).

Neither higher engagement in work physical activity nor regular walking showed a significant trend towards lower MPO concentrations. After additional adjustment for interleukin-6, the major cytokine released during exercise, the point estimates only marginally changed and the inverse association between leisure-time physical activity and MPO remained significant ($P_{trend} = 0.011$). Regarding ox-LDL, no inverse association was observed for any of the investigated physical activity domains ($P_{trend} = 0.162–0.803$). The relationship between physical activity and oxidative stress levels was not modified by sex, when respective interaction terms were entered into the regression model ($p > 0.05$).

These results were confirmed by a further sub-analysis in S2 ($n = 742$) using the MOSPA questionnaire for a more specific assessment of physical activity (Table 2). As shown in the previous analysis among 1820 participants, leisure-time physical activity was significantly and inversely related with MPO ($P_{trend} = 0.006$), whereas work, transportation, or household physical activity were not.

5. Discussion

We examined the association of domain-specific physical activity with both MPO and ox-LDL levels in a large population-based sample of middle-aged participants. Our findings suggest an inverse association between regular leisure-time physical activity and MPO levels. This relationship was independent of age, sex, survey, education, body mass index, alcohol consumption, smoking status, actual hypertension, diabetes, total-to-HDL cholesterol ratio, dietary habits, and self-reported limited PA due to health problems.

Table 2
Adjusted geometric means[a] (95% CI) of ox-LDL and MPO according to domain and physical activity level from the MOSPA questionnaire (survey S2).

	No	Light	Moderate	Vigorous	P_{trend}
Leisure-time	$n = 84$	$n = 308$	$n = 259$	$n = 91$	
Ox-LDL (U/ml)	91.5 (86.3–97.1)	92.9 (88.7–97.1)	90.8 (86.8–95.1)	91.7 (86.3–97.5)	0.593
MPO (μg/ml)	133.3 (120.7–147.1)	118.2 (109.6–127.6)	114.1 (105.6–123.1)	113.2 (102.2–125.4)	0.006
Work[b]	–	$n = 37$	$n = 341$	–	
Ox-LDL (U/ml)	–	88.9 (80.5–98.2)	90.0 (84.9–95.5)	–	0.775
MPO (μg/ml)	–	125.7 (106.8–148.0)	116.1 (105.3–128.0)	–	0.282
Transportation	$n = 264$	$n = 69$	$n = 242$	$n = 167$	
Ox-LDL (U/ml)	90.4 (86.4–94.5)	95.2 (89.3–101.6)	91.5 (87.4–95.9)	92.6 (88.0–97.4)	0.386
MPO (μg/ml)	121.8 (112.9–131.4)	117.8 (105.6–131.3)	117.4 (108.5–127.0)	116.1 (106.6–126.5)	0.198
Household	$n = 301$	$n = 391$	$n = 50$	–	
Ox-LDL (U/ml)	92.8 (88.7–97.0)	90.8 (87.0–94.9)	91.6 (84.8–98.9)	–	0.459
MPO (μg/ml)	118.6 (109.9–127.9)	119.0 (110.6–128.1)	119.8 (105.2–136.5)	–	0.870
Total	–	$n = 57$	$n = 448$	$n = 237$	
Ox-LDL (U/ml)	–	88.9 (82.9–95.3)	91.9 (88.2–95.8)	92.6 (88.3–97.0)	0.342
MPO (μg/ml)	–	134.2 (119.4–150.8)	117.3 (109.4–125.8)	116.4 (107.6–125.9)	0.093

[a] Adjusted for age, sex, education, body mass index, alcohol consumption, smoking status, actual hypertension, diabetes, total-to-HDL cholesterol ratio, dietary habits, and self-reported limited PA due to health problems.
[b] Analyses restricted to working participants ($n = 378$).

For ox-LDL, no significant association could be found with any of the investigated domains of physical activity. As MPO induces the oxidation of LDL, a similar reduction of ox-LDL would be expected; however, MPO is only one of several factors having an impact on the oxidation of LDL, which may explain the lack of association between MPO and ox-LDL (Spearman correlation coefficient $r = 0.08$). Furthermore, differing detectabilities of these markers in serum samples may explain the observed results.

It is striking that, according to our data, even the engagement in light leisure-time activities appears to substantially decrease levels of MPO levels. Previous studies have emphasized that persons will particularly benefit from moderate leisure-time activities such as jogging [6]. We can confirm and extend this evidence by ascribing beneficial effects to individuals with any amount of physical activity, which appears to reduce MPO in our study population. We did not find increasing MPO in the vigorous physical activity group, probably because this degree of high physical activity is not strenuous enough to cause substantial oxidative stress as observed in studies of excessive exercise.

Even though a number of studies have concentrated on the adaptation processes of exercise training programs [9,10], the mechanisms of how regular physical activity affects reactive oxygen species are not yet fully understood. However, the most notable adaptations to regular aerobic exercise include an increase in plasma antioxidant capacity and an enhanced resistance of LDL into its oxidized state.

These observations are confirmed in murine models. Laufs and colleagues tested the difference between sedentary mice in a regular cage as opposed to mice housed in cages equipped with running wheels. Because mice were not forced to run, no additional stress could have confounded the results. Active mice ran an average of 4.9 km per day. In sedentary mice, the investigators found greater levels of NADPH oxidase, an enzyme complex which produces reactive oxygen species and therefore contributes to the manifestation of atherosclerosis and endothelial dysfunction [14].

Apart from the present analysis, a cross-sectional study among 488 Spanish females found that leisure-time physical activity enhanced endogenous antioxidant activity (superoxide dismutase, glutathione peroxidase), but no association was observed with lipid peroxides. Similar results were found when household activities and leisure-time physical activity were added up to a total physical activity score [15].

The strengths of our study are the large sample size, its population-based design and the careful evaluation of oxidative stress markers as well as other cardiovascular risk factors at baseline. Limitations include the cross-sectional design, physical activity assessment based on self-report as well as the availability of only one measurement of ox-LDL and MPO levels.

Despite these limitations, we conclude that engagement in regular leisure-time physical activity appears to counterbalance the production of cell-damaging free radicals. More data from large epidemiological studies are needed to confirm these results in order to ascribe decreased oxidative stress levels as additional benefits of regular leisure-time physical activity.

Conflict of interest

None of the authors declare any actual or potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.07.125.

References

[1] Holvoet P, Jenny NS, Schreiner PJ, et al. The relationship between oxidized LDL and other cardiovascular risk factors and subclinical CVD in different ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2007;194(1):245–52.
[2] Meisinger C, Baumert J, Khuseyinova N, et al. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. Circulation 2005;112(5):651–7.
[3] Strobel NA, Fassett RG, Marsh SA, et al. Oxidative stress biomarkers as predictors of cardiovascular disease. Int J Cardiol 2011;147(2):191–201.
[4] Hulthe J, Fagerberg B. Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR Study). Arterioscler Thromb Vasc Biol 2002;22(7):1162–7.
[5] Karakas M, Koenig W, Zierer A, et al. Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: results from the MONICA/KORA Augsburg Study. J Intern Med 2011;(May) [Epub ahead of print].
[6] Aldred S. Oxidative and nitrative changes seen in lipoproteins following exercise. Atherosclerosis 2007;192(2):1–8.
[7] Powers SK, Nelson WB, Hudson MB. Exercise-induced oxidative stress in humans: cause and consequences. Free Radic Biol Med 2010 (Dec)[Epub ahead of print].
[8] Fisher-Wellman K, Bloomer RJ. Acute exercise and oxidative stress: a 30 year history. Dyn Med 2009;8:1.
[9] Elosua R, Molina L, Fito M, et al. Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. Atherosclerosis 2003;167(2):327–34.
[10] Ziegler S, Schaller G, Mittermayer F, et al. Exercise training improves low-density lipoprotein oxidability in untrained subjects with coronary artery disease. Arch Phys Med Rehabil 2006;87(2):265–9.
[11] Lowel H, Doring A, Schneider A, et al. The MONICA Augsburg surveys – basis for prospective cohort studies. Gesundheitswesen 2005;67(Suppl. 1):S13–8.
[12] Autenrieth CS, Baumert J, Baumeister SE, et al. Association between domains of physical activity and all-cause, cardiovascular and cancer mortality. Eur J Epidemiol 2011;26(2):91–9.
[13] Keil U, Stieber J, Doring A, et al. The cardiovascular risk factor profile in the study area Augsburg. Results from the first MONICA survey 1984/85. Acta Med Scand Suppl 1988;728:119–28.
[14] Laufs U, Wassmann S, Czech T, et al. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25(4):809–14.
[15] Covas MI, Elosua R, Fito M, et al. Relationship between physical activity and oxidative stress biomarkers in women. Med Sci Sports Exerc 2002;34(5):814–9.

Supplementary material: Methods section

Covariables

Information on smoking and drinking habits, medical history, education, and self-estimated limited physical activity due to health problems (yes/no) was assessed through standardized face-to-face interviews. Alcohol intake was categorized into no, moderate (for men: >0 - <40 g/day, for women: >0 - <20 g/day) and high alcohol consumption (for men: ≥40 g/day, for women: ≥20 g/day). Smoking levels were disposed into the following categories: current cigarette smokers, ex-smokers and never smokers. Education status was dichotomized into low (≤11 years of school) and high educational level (≥12 years of school).

Blood pressure (BP) and body-mass index (BMI, weight in kg/(height in m)^2) were measured by trained medical staff. BP was measured with a Hawksley Random Zero sphygmomanometer. Three BP recordings were taken from each individual after completion of the interview, i.e. after being at rest in a sitting position for an average of 30 minutes. The BP results provided are based on the mean of the second and third BP recordings. Further details on the measurement procedures are reported elsewhere [1]. Actual hypertension was defined as blood pressure values ≥140/90 mmHg and/or the usage of antihypertensive medication given that the subjects were aware that they had hypertension [1].

Total cholesterol was measured by an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany) and high-density lipoprotein (HDL) cholesterol after precipitation with phosphotungstic acid/Mg^{2+} (Boehringer Mannheim, Mannheim, Germany)

Data on dietary habits were collected through a 24-item food frequency list (FFL). Based on the responses for 16 items[1], a healthy diet score ranging from 3 to 27 was calculated for each participant, and the validity of the FFL proved to be sufficient on a group level [2,3]. For the present analysis, the following three categories were used: unhealthy diet score (≤13), normal diet score (14-15), healthy diet score (≥16).

Further information on physical activity variables

The questions on leisure-time physical activity, work physical activity and walking were derived from the German Cardiovascular Prevention Study conducted between 1979 and 1995. By using a physical activity diary as comparison, these questions have been validated in our population [4] and have also been used in various other publications [5,6].

The MOSPA questionnaire which was used in our subanalysis of 742 participants from the second survey was provided by the World Health Organization and has also been validated [7,8].

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[1] Meat (without sausages), sausages, ham; poultry, fish; potatoes; pasta; rice; salad or vegetable, raw; vegetable, cooked; fresh fruit; chocolate, chocolates; cakes, pastries, biscuits; salted snacks such as salted peanuts, crisps, and others; whole grain bread, black bread, crispbread; flaked oats, muesli, cornflakes; eggs.

References

[1] Hense HW, Filipiak B, Döring A, et al. Ten year trends of cardiovascular risk factors in the MONICA Augsburg region in southern Germany: Results from the 1984/1985, 1989/1990, and 1994/1995 surveys. CVD Prevention 1998;1(4):318–27.

[2] Winkler G, Schwertner B, Döring A. Kurzmethoden zur Charakterisierung des Ernährungsmusters: Einsatz und Auswertung eines Food-Frequency-Fragebogens. Ernährungs-Umschau 1995;42(8):289-291.

[3] Winkler G. Döring A. Validation of a short qualitative food frequency list used in several German large scale surveys. Z Ernährungswiss 1998;37(3):234-241.

[4] Stender M, Döring A, Hense HW, et al. Vergleich zweier Methoden zur Erhebung der körperlichen Aktivität. Soz Präventivmed 1991;36(3):176-183.

[5] Koenig W, Sund M, Döring A, et al. Leisure-Time Physical Activity but Not Work-Related Physical Activity Is Associated With Decreased Plasma Viscosity: Results From a Large Population Sample. Circulation 1997; 95(2): 335-341.

[6] Meisinger C, Löwel H, Thorand B, et al. Leisure time physical activity and the risk of type 2 diabetes in men and women from the general population. The MONICA/KORA Augsburg Cohort Study. Diabetologia. 2005;48(1):27-34.

[7] Roeykens J, Rogers R, Meeusen R, et al. Validity and reliability in a Flemish population of the WHO-MONICA Optional Study of Physical Activity Questionnaire. Med Sci Sports Exerc 1998;30(7):1071-5.

[8] Iqbal R, Rafique G, Badruddin S, et al. Validating MOSPA questionnaire for measuring physical activity in Pakistani women. Nutr J 2006;5:18.

Supplementary Table 1. Percentages and means (S.D.) of covariables according to leisure-time physical activity.

	No	Low	Moderate	High	*p*-value
No. of subjects	n = 857	n = 269	n = 431	n = 263	
Men (%)	46.6	51.3	45.7	66.5	<0.001
High alcohol consumption (%)*	26.0	28.3	25.6	25.5	0.003
Actual hypertension (%)	45.6	42.8	35.7	38.8	0.006
Unhealthy diet (%)†	33.3	30.9	27.4	34.6	0.123
Diabetes (%)	6.4	4.8	2.3	3.8	0.011
Low education (%)‡	82.8	74.7	71.2	64.3	<0.001
Limited PA due to health problems (%)	34.7	29.7	23.4	17.9	<0.001
Smoker (%)	25.9	26.4	21.8	24.0	<0.001
Age (years)	54.7 (10.1)	51.0 (10.2)	49.6 (10.3)	50.3 (10.7)	<0.001
BMI (kg/m^2)	27.6 (4.2)	27.2 (4.1)	26.4 (3.9)	26.5 (3.6)	<0.001
Total-to-HDL cholesterol ratio	4.61 (1.65)	4.60 (1.91)	4.48 (1.71)	4.65 (1.73)	0.576

* ≥40g/day for men, ≥20g/day for women.
† ≤13 in the diet score, based on the food frequency questionnaire.
‡ ≤11 years of school.

4.2 Association between physical activity and risk of stroke subtypes: The Atherosclerosis Risk in Communities (ARIC) Study

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Association between Physical Activity and Risk of Stroke Subtypes: The Atherosclerosis Risk in Communities Study

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Key Words
Cerebrovascular disease · Stroke subtypes · Exercise · Epidemiology · Prevention

Abstract
Background: The relationship between stroke subtypes and physical activity is unclear. ***Methods:*** Using data from 13,069 men and women aged 45–64 years who participated in the Atherosclerosis Risk in Communities Study, physical activity was assessed by self-report using the Baecke questionnaire at baseline (1987–1989). The American Heart Association's ideal cardiovascular health guidelines served as a basis for the calculation of three physical activity categories: poor, intermediate, and ideal. Stroke and its subtypes were ascertained from physician review of medical records. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox regression models. ***Results:*** During a median follow-up of 18.8 years, a total of 648 incident ischemic strokes occurred. Significant inverse associations were found between physical activity categories and total, total ischemic, and nonlacunar stroke in adjusted models (age, sex, race-center, education, cigarette-years). Compared with poor physical activity, the adjusted HR (95% CI) for ideal physical activity were 0.78 (0.62–0.97) for total, 0.76 (0.59–0.96) for total ischemic, 0.85 (0.51–1.40) for lacunar, 0.77 (0.47–1.27) for cardioembolic, and 0.71 (0.51–0.99) for nonlacunar stroke. Additional adjustments for waist-to-hip ratio, systolic blood pressure, antihypertensive medication, diabetes, left ventricular hypertrophy and laboratory parameters attenuated the HR. Further sex- and race-specific analyses revealed that the association was predominantly observed among males and among African-Americans. ***Conclusion:*** These data suggest a tendency toward a reduced risk of total, total ischemic, and nonlacunar stroke with higher levels of physical activity.

Introduction

Although cardiovascular disease mortality rates have declined over the past several decades in the United States, the burden of stroke still remains high. Each year,

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approximately 795,000 new or recurrent stroke events occur in the United States [1]. A number of modifiable risk factors have been linked to an increased risk of stroke, including high blood pressure, cigarette smoking, and physical inactivity [1, 2]. To date, empirical data on whether physical activity helps in reducing stroke risk have yielded mixed results. Even though several meta-analyses [3–5] and other studies [6–9] generally found evidence of some protective effect of physical activity in the prevention of stroke, other studies did not [10, 11].

Studies examining the association of physical activity with stroke subtypes may refine our understanding of its potential in modifying stroke risk. Little information is available, however, on the association between ischemic stroke subtypes (lacunar, cardioembolic, nonlacunar thrombotic) and physical activity, as previous work on subtypes has mainly concentrated on hemorrhagic stroke subtypes (intracerebral, subarachnoid) and their relationship with physical activity [6, 7]. In previous work from the Atherosclerosis Risk in Communities (ARIC) Study, some risk factors varied by ischemic stroke subtype [12], and physical activity was weakly associated with total ischemic stroke risk [10]. The role of physical activity on risk of stroke subtypes was not evaluated in that study, due to insufficient number of cases at that time.

In the present study, we sought to clarify in detail the relationship between physical activity and stroke subtypes in a large prospective cohort of men and women aged 45–64 years at baseline participating in the ARIC Study.

Methods

Study Population

The ARIC Study is a prospective population-based cohort study comprising 15,792 adults aged 45–64 years at recruitment in 1987–1989 [13]. Cohort participants were selected from four US communities: Forsyth County, N.C.; Jackson, Miss.; Minneapolis, Minn., and Washington County, Md. Participants completed the first exam between 1987 and 1989. Baseline data served as a basis for the present study, and participants were followed up through 2007 via annual telephone interviews. The study was approved by the institutional review board of the University of North Carolina as well as the other study centers and all participants provided informed consent.

Physical Activity Measurements

Physical activity was assessed at the baseline exam through an interviewer-administered Baecke questionnaire [14]. Minor modifications to the original version of the Baecke questionnaire were made as detailed elsewhere [15] and are only briefly described here. On the baseline survey, participants were asked to report the amount of physical activity performed during leisure and sport. The participants' indications allowed the calculation of sport and leisure Baecke score ranging from 1 (low) to 5 (high). Leisure activities were assessed through 4 questions on walking, biking, television viewing and time spent commuting (walking/biking) to and from work or shopping. The sport score was based on 3 questions regarding the frequency of overall sport and exercise participation, and frequency of sweating. In addition, a fourth element on frequency, intensity and duration of up to 4 sport activities also contributed to the score. Furthermore, based on the guidelines of the compendium of physical activities [16], minutes per week of moderate or vigorous exercise were calculated from the Baecke sport questions, incorporating the number of months an individual engaged in the activity annually. The validity and reliability of the Baecke questionnaire has been reported elsewhere [17].

In order to determine the difference between participants who reached the necessary minimum of physical activity and those who did not, minutes per week of exercise were classified according to the American Heart Association's ideal cardiovascular health guidelines for adults aged 20 years and above [18]. (1) Poor physical activity was defined as 0 min/week of moderate or vigorous exercise. (2) Intermediate physical activity was defined as 1–149 min/week of moderate intensity or 1–74 min/week of vigorous intensity or 1–149 min/week of moderate and vigorous intensity. (3) Ideal physical activity was defined as ≥150 min/week of moderate intensity or ≥75 min/week of vigorous intensity or ≥150 min/week of moderate and vigorous intensity.

Ascertainment of Stroke Events

Through annual phone interviews, follow-up examinations, surveillance of hospital discharges, and deaths in the ARIC communities, hospitalized stroke events and out-of-hospital fatal strokes among ARIC cohort participants were identified [13]. For the present analysis, hospitalized stroke events which occurred between baseline measurements (visit 1) and December 31, 2007 were included.

Evidence of stroke was ascertained via hospital reports if the discharge diagnosis contained a cerebrovascular disease code (International Classification of Diseases, 9th Revision codes 430–438), if a cerebrovascular procedure was noted in the discharge summary, or if the computed tomography (CT) or magnetic resonance imaging (MRI) report showed evidence of cerebrovascular disease. Medical records for potential stroke events were then sent to a central ARIC office for abstraction by a single nurse. Each record was abstracted for number, type, and severity of neurological deficits and supporting angiographic, CT, MRI, spinal tap, or autopsy evidence. Each suspected stroke event was classified by National Survey of Stroke criteria using a computer algorithm as well as a physician reviewer [19]. When the algorithm and physician review disagreed, another physician reviewer was consulted as an adjudicator. Quality assurance for ascertainment and classification of stroke are described in detail elsewhere [20]. In brief, a subclassification of definite or probable hospitalized ischemic (cardioembolic or thrombotic), or hemorrhagic stroke was used based on the level of certainty assessed through neuroimaging studies and autopsy, when available.

If a CT or MRI revealed acute brain infarction or showed no evidence of hemorrhage, a stroke was categorized as ischemic. Using neuroimaging results, subcategories of all definite ischemic strokes (lacunar, cardioembolic, nonlacunar thrombotic) were determined [12, 20].

Covariates

Information on risk factors was obtained through standardized questionnaires, clinical examination, and laboratory measurements. Cigarette-years of smoking was defined as the average number of cigarettes per day times the number of years smoked. Educational level was dichotomized into high (>high school) and low education (≤high school). Body mass index was calculated as measured weight in kilograms divided by height in meters squared. The ratio of waist and hip circumferences was also calculated as a measure of fat distribution. Three successive measurements of systolic and diastolic blood pressure were taken using a random-zero sphygmomanometer after a 5-min rest. For the present analysis, the average of the two last measurements was used. Antihypertensive medication use was defined as having taken hypertension-lowering medication in the past 2 weeks. Prevalent diabetes was defined as nonfasting glucose level ≥200 mg/dl, fasting glucose level ≥126 mg/dl, medication treatment for or history of diabetes. Left ventricular hypertrophy was determined by Cornell voltage criteria, after a 12-lead electrocardiography tracing had been obtained [21]. Blood levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein(a), fibrinogen and von Willebrand factor, and white blood cell count were measured centrally by standard methods [22]. Prevalent coronary heart disease and stroke, for exclusion, was defined as one of the following: self-report of physician-diagnosed myocardial infarction or stroke, prior myocardial infarction by electrocardiography, or having had coronary revascularization surgery.

Statistical Analyses

Due to small numbers, we excluded participants who were not African-American or white (n = 48) and African-Americans from Minneapolis (n = 22) or Washington County (n = 33). Participants with missing data on physical activity or any of the covariates, as well as participants with a positive history of stroke or CHD were sequentially removed from the dataset (n = 2,620). The final analysis cohort consisted of 13,069 ARIC participants.

General linear and logistic regression models were used to assess trends across physical activity quartiles of baseline risk factors for continuous and categorical variables, respectively. Multivariate Cox proportional hazards models were used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident stroke types with physical activity categories. Three Cox regression models with the following covariates were evaluated: (1) basic adjusted model (adjusted for age, sex, and race-center), (2) partially adjusted model (additional adjustment for educational level and cigarette-years), and (3) fully adjusted model [additionally adjusted for waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, von Willebrand factor, and white blood cell count]. In addition, sex- and race-specific analyses were performed. p for trend was calculated by including the physical activity variable in the model as a continuous variable. SAS version 9.2 (SAS Institute, Inc., Cary, N.C., USA) was used to perform all analyses.

Results

Over a median follow-up of 18.8 years, 648 incident ischemic strokes occurred. Of those, 144 were lacunar, 150 were cardioembolic, and 354 were nonlacunar. Generally, participants in the higher sport quartiles had higher education, lower body mass index, and were less prone to chronic conditions such as diabetes or left ventricular hypertrophy compared to those in the lower quartiles of sport scores (table 1). Laboratory measures consistently declined with increasing sport quartiles except for high-density and low-density lipoprotein cholesterol. Compared to participants not having suffered from a stroke event, mean sport scores were lower in any stroke type (data not shown). The lowest mean baseline score was found in participants who subsequently suffered a hemorrhagic stroke (2.32).

As shown in table 2, the incidence rate per 1,000 person-years was lowest in the ideal physical activity category for total and total ischemic stroke.

Significant risk reductions in total and total ischemic stroke were observed with increasing physical activity level in both the basic adjusted model and the partially adjusted model (p for trend <0.05). In the partially adjusted model, HR (95% CI) for the highest versus the lowest physical activity category for total and total ischemic stroke were 0.78 (0.62–0.97) and 0.76 (0.59–0.96), respectively. Sex-specific analyses revealed that this association was much stronger in men, and that no significant relation between physical activity and neither total nor total ischemic stroke could be observed for women. In the fully adjusted model, additional adjustments were performed for variables that were likely biological intermediates, such as systolic blood pressure or lipids. We observed an attenuation towards the null for the total analytical sample; however, among men, the association between physical activity and total stroke remained significant, even in the fully adjusted model.

A slightly different pattern is shown in table 3 for the ischemic stroke subtypes. In the basic adjusted model and the partially adjusted model, only nonlacunar stroke was significantly associated with physical activity in the total sample and among men. Compared to the reference group poor activity in the partially adjusted model, an HR of 0.71 (0.51–0.99) was observed for ideal activity in the total sample. However, in the fully adjusted model, no inverse relationship between physical activity and any of the ischemic stroke subtypes could be observed.

In an additional subanalysis, we performed race-specific analysis. The beneficial effects of higher physical ac-

Table 1. Means (SD) and percentages of baseline risk factors by quartiles[a] of the Baecke sport score

	Q1 (n = 3,692)	Q2 (n = 3,076)	Q3 (n = 3,677)	Q4 (n = 2,624)	p value
Age, years	53.7 (5.7)	54.1 (5.7)	54.2 (5.8)	54.0 (5.8)	0.003
Men, %	35.5	39.0	44.9	55.8	<0.001
Blacks, %	36.6	30.6	18.9	13.0	<0.001
High education, %	36.7	38.8	48.8	57.6	<0.001
Cigarette-years	306.6 (437.0)	315.2 (439.7)	284.3 (399.8)	298.6 (388.8)	0.018
Body mass index	28.4 (6.0)	28.0 (5.6)	27.3 (4.9)	26.5 (4.2)	<0.001
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001
Systolic blood pressure, mm Hg	122.9 (19.8)	121.7 (18.5)	120.1 (17.8)	118.3 (17.2)	<0.001
Antihypertensive mediation use, %	32.8	30.1	25.7	20.0	<0.001
Diabetes, %	13.0	11.1	9.4	6.9	<0.001
Left ventricular hypertrophy, %	2.7	2.2	1.5	1.3	<0.001
HDL cholesterol, mg/dl	52.6 (17.1)	52.3 (16.5)	51.9 (16.8)	53.0 (17.3)	0.073
LDL cholesterol, mg/dl	137.1 (40.0)	137.8 (41.1)	137.8 (38.0)	135.4 (37.2)	0.061
Lipoprotein(a), μg/ml[b]	62.5 (3.2)	56.7 (3.2)	54.6 (3.2)	49.4 (3.2)	<0.001
Fibrinogen, mg/dl	311.8 (69.6)	305.9 (65.4)	298.6 (60.0)	288.8 (59.0)	<0.001
von Willebrand factor	121.6 (51.2)	116.6 (46.6)	115.1 (46.2)	113.1 (44.6)	<0.001
White blood cell count, cells/mm^3	6,162.6 (2,000.0)	6,115.4 (1,893.8)	6,056.2 (1,984.2)	5,963.7 (1,759.5)	<0.001

HDL = High-density lipoprotein; LDL = low-density lipoprotein.
[a] Cutoff points for the approximated quartiles were 1.75/2.25/3.0 of the Baecke sport score.
[b] Geometric mean (antilog of SD).

tivity levels in model 2 are predominantly observed among African-Americans for total, total ischemic, and nonlacunar stroke, whereas no significant relations were observed for Caucasians (online suppl. table S1 and S2; for all online supplementary material, see www.karger.com/doi/10.1159/000342151).

Examining the effect of quartiles of sport and leisure scores on stroke and its subtypes in the total sample revealed a weaker association, but a trend in risk reductions across sport quartiles for total, total ischemic stroke, and nonlacunar stroke was generally still observed (online suppl. table S3 and S4).

Discussion

In this prospective cohort study, we found that physical activity was inversely associated with ischemic stroke and some subtypes among middle-aged men and women. The observed inverse associations between physical activity and total, total ischemic, and nonlacunar stroke in both the basic adjusted and the partially adjusted model were no longer statistically significant in the fully adjusted models, that accounted for potential intermediates. The observed associations were stronger in men and in African-Americans. In addition, we found that the overall effect of physical activity is consistent across stroke subtypes.

Evidence in the literature as to the role of physical activity in stroke risk is mixed. Three meta-analyses have shown relatively clear inverse associations between physical activity and stroke risk [3–5], while other studies have not [10, 11]. Our results are generally in accordance with previous work supporting a beneficial effect from physical activity by revealing a significant trend towards lower stroke risk with higher levels of physical activity. In particular, our results are very similar to recent data from the Northern Manhattan Study, in which moderate to heavy physical activity was found to be associated with ischemic stroke risk in men among 238 ischemic stroke cases during 9.1 years of follow-up [9]. In the Women's Health Study, a relationship of borderline significance was found between leisure physical activity and total as well as total ischemic stroke in women [23]. Likewise, in the Nurses' Health Study, quintiles of leisure physical activity were significantly associated with lower risks of total and ischemic stroke, but not hemorrhagic stroke, after multivariable adjustments and during 8 years of follow-up [6]. However, we did not find an inverse association between physical activity and stroke among women.

Table 2. Multivariable adjusted HR and 95% CI for physical activity and stroke

	Poor physical activity	Intermediate physical activity	Ideal physical activity	p for trend
Total sample				
Total stroke				
No. of cases	496	147	97	
Person-years	12,7263.5	57,604.0	40,703.3	
Incidence rate[a]	3.90 (3.57–4.26)	2.55 (2.17–3.00)	2.38 (1.95–2.91)	
Model 1[b]	1	0.78 (0.65–0.95)	0.72 (0.57–0.90)	<0.001
Model 2[c]	1	0.83 (0.68–1.00)	0.78 (0.62–0.97)	0.010
Model 3[d]	1	0.89 (0.73–1.07)	0.85 (0.68–1.07)	0.104
Total ischemic stroke				
No. of cases	430	135	83	
Person-years	12,7563.6	57,653.9	40,773.3	
Incidence rate[a]	3.37 (3.07–3.71)	2.34 (1.98–2.77)	2.04 (1.64–2.52)	
Model 1[b]	1	0.82 (0.67–1.00)	0.70 (0.55–0.89)	0.002
Model 2[c]	1	0.87 (0.71–1.06)	0.76 (0.59–0.96)	0.016
Model 3[d]	1	0.93 (0.76–1.14)	0.84 (0.65–1.07)	0.142
Men				
Total stroke				
No. of cases	213	77	58	
Person-years	45,980.5	26,126.6	22,739.3	
Incidence rate[a]	4.63 (4.05–5.30)	2.95 (2.36–3.68)	2.55 (1.97–3.30)	
Model 1[b, e]	1	0.73 (0.56–0.96)	0.64 (0.48–0.87)	0.001
Model 2[c, e]	1	0.76 (0.58–0.99)	0.68 (0.50–0.91)	0.005
Model 3[d, e]	1	0.80 (0.61–1.05)	0.76 (0.56–1.02)	0.042
Total ischemic stroke				
No. of cases	190	72	53	
Person-years	46,084.1	26,141.5	22,785.7	
Incidence rate[a]	4.12 (3.58–4.75)	2.75 (2.19–3.47)	2.33 (1.78–3.04)	
Model 1[b, e]	1	0.76 (0.58–1.00)	0.66 (0.48–0.89)	0.004
Model 2[c, e]	1	0.79 (0.60–1.05)	0.69 (0.51–0.95)	0.014
Model 3[d, e]	1	0.84 (0.63–1.11)	0.78 (0.57–1.07)	0.090
Women				
Total stroke				
No. of cases	283	70	39	
Person-years	81,283.0	31,477.4	17,964.0	
Incidence rate[a]	3.48 (3.10–3.91)	2.22 (1.76–2.81)	2.17 (1.59–2.97)	
Model 1[b, e]	1	0.83 (0.64–1.09)	0.80 (0.57–1.13)	0.109
Model 2[c, e]	1	0.90 (0.69–1.19)	0.88 (0.63–1.24)	0.364
Model 3[d, e]	1	0.98 (0.75–1.29)	0.94 (0.67–1.33)	0.735
Total ischemic stroke				
No. of cases	240	63	30	
Person-years	81,479.5	31,512.3	17,987.6	
Incidence rate[a]	2.95 (2.60–3.34)	2.00 (1.56–2.56)	1.67 (1.17–2.39)	
Model 1[b, e]	1	0.89 (0.67–1.19)	0.74 (0.50–1.08)	0.102
Model 2[c, e]	1	0.97 (0.72–1.29)	0.81 (0.55–1.19)	0.323
Model 3[d, e]	1	1.05 (0.79–1.41)	0.87 (0.59–1.28)	0.654

[a] Incidence rate per 1,000 person-years. [b] Adjusted for age, sex and race-center. [c] Adjusted for age, sex, race-center, cigarette-years and education. [d] Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, van Willebrand factor and white blood cell count. [e] Not adjusted for sex.

Table 3. Multivariable adjusted HR and 95% CI for physical activity and ischemic stroke subtypes

	Poor physical activity	Intermediate physical activity	Ideal physical activity	p for trend
Total sample				
Lacunar stroke				
No. of cases	101	24	19	
Model 1[a]	1	0.71 (0.45–1.13)	0.74 (0.45–1.22)	0.132
Model 2[b]	1	0.79 (0.50–1.25)	0.85 (0.51–1.40)	0.371
Model 3[c]	1	0.85 (0.54–1.36)	0.95 (0.57–1.59)	0.695
Cardioembolic stroke				
No. of cases	100	30	20	
Model 1[a]	1	0.78 (0.51–1.18)	0.72 (0.44–1.18)	0.130
Model 2[b]	1	0.82 (0.54–1.25)	0.77 (0.47–1.27)	0.237
Model 3[c]	1	0.87 (0.57–1.34)	0.83 (0.50–1.37)	0.402
Nonlacunar stroke				
No. of cases	229	81	44	
Model 1[a]	1	0.87 (0.67–1.13)	0.66 (0.48–0.92)	0.014
Model 2[b]	1	0.91 (0.70–1.19)	0.71 (0.51–0.99)	0.046
Model 3[c]	1	0.99 (0.76–1.28)	0.78 (0.56–1.08)	0.187
Men				
Lacunar stroke				
No. of cases	44	13	12	
Model 1[a, d]	1	0.65 (0.35–1.23)	0.66 (0.35–1.28)	0.152
Model 2[b, d]	1	0.71 (0.37–1.34)	0.74 (0.38–1.43)	0.286
Model 3[c, d]	1	0.74 (0.39–1.40)	0.80 (0.41–1.55)	0.403
Cardioembolic stroke				
No. of cases	39	14	15	
Model 1[a, d]	1	0.68 (0.37–1.27)	0.87 (0.47–1.60)	0.504
Model 2[b, d]	1	0.70 (0.37–1.30)	0.89 (0.48–1.65)	0.570
Model 3[c, d]	1	0.71 (0.38–1.34)	0.96 (0.51–1.79)	0.729
Nonlacunar stroke				
No. of cases	107	45	26	
Model 1[a, d]	1	0.82 (0.57–1.16)	0.56 (0.36–0.87)	0.009
Model 2[b, d]	1	0.84 (0.59–1.21)	0.59 (0.38–0.92)	0.019
Model 3[c, d]	1	0.91 (0.63–1.31)	0.67 (0.43–1.04)	0.084
Women				
Lacunar stroke				
No. of cases	57	11	7	
Model 1[a, d]	1	0.78 (0.40–1.52)	0.83 (0.37–1.83)	0.486
Model 2[b, d]	1	0.90 (0.46–1.76)	0.96 (0.43–2.14)	0.838
Model 3[c, d]	1	0.97 (0.50–1.91)	1.14 (0.51–2.56)	0.814
Cardioembolic stroke				
No. of cases	61	16	5	
Model 1[a, d]	1	0.90 (0.51–1.59)	0.47 (0.19–1.18)	0.126
Model 2[b, d]	1	0.98 (0.55–1.73)	0.52 (0.21–1.31)	0.225
Model 3[c, d]	1	1.06 (0.59–1.88)	0.54 (0.21–1.37)	0.307
Nonlacunar stroke				
No. of cases	122	36	18	
Model 1[a, d]	1	0.93 (0.64–1.37)	0.82 (0.50–1.35)	0.428
Model 2[b, d]	1	0.99 (0.68–1.46)	0.88 (0.53–1.45)	0.665
Model 3[c, d]	1	1.08 (0.73–1.60)	0.94 (0.56–1.56)	0.959

[a] Adjusted for age, sex and race-center. [b] Adjusted for age, sex, race-center, cigarette-years and education. [c] Adjusted for age, sex, race-center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, van Willebrand factor and white blood cell count. [d] Not adjusted for sex.

With almost a decade of longer follow-up time and more stroke cases, we were able to evaluate the role of physical activity on risk of ischemic stroke subtypes to better specify the relationship to physical activity. Indeed, previous work has examined hemorrhagic stroke subtypes and reported significant associations between leisure activities and both subarachnoid and intracerebral stroke [7]. But, to our knowledge, no study has specifically examined the impact of physical activity on ischemic stroke subtypes. In other ARIC studies on ischemic stroke subtypes, it has been shown that the impact of traditional and novel risk factors of stroke as well as carotid artery wall thickness [24] may vary between lacunar, cardioembolic and nonlacunar thrombotic stroke [12]. Obesity measures such as body mass index and waist-to-hip ratio were positively related with all three investigated ischemic stroke subtypes [25]. As to the results of our study, the impact of physical activity did not vary according to ischemic stroke subtypes. Our data suggest that the somewhat inconsistent findings on the association between physical activity and stroke risk in the literature may not be due to differences in varying proportion of stroke subtypes across studies.

A possible explanation for a similar association across ischemic stroke subtypes is that factors such as vascular risk factors play a key role in explaining the reduced risk of all investigated stroke types, as physical activity is commonly known to lower risk of atherosclerosis and thrombosis [26]. It is therefore challenging to isolate the single effect of physical activity, and the possibility that physical activity acts through those risk factors is plausible. Indeed, the results of our baseline characteristics depict that physical activity is significantly associated with many risk factors for stroke. These results along with the continuous attenuation of the inverse association of physical activity and stroke subtypes between the basic adjusted, partially adjusted as well as fully adjusted model support this assumption.

The strengths of our study include a long follow-up time and the separate analysis of ischemic stroke subtypes. Only very few studies have looked at ischemic stroke subtypes as outcome [12, 24, 25], but have not reported on physical activity as an exposure variable so far. In addition, ARIC is a well-characterized cohort with good comprehensive analyses through annual phone contact and surveillance of community hospitals. However, several limitations need to be considered. First, physical activity measures were based on self-report, which may have led to reporting bias and misclassification. Second, although stroke subtypes were carefully evaluated through neuroimaging studies and clinical features [20], misclassification in some cases may have occurred and an over- or underestimation of the association between physical activity and stroke subtypes cannot be fully ruled out. Third, the number of cases for each ischemic stroke subtype was relatively small. Fourth, although physical activity information was collected before the occurrence of stroke events, there may be individuals who had modified their exercise habit because of their health status, which might have distorted the true association.

In conclusion, our work supports the body of evidence concerning a tendency towards a decreased risk of stroke associated with higher physical activity levels. The present study also provides novel information on the role of physical activity and risk of ischemic stroke subtypes. With nonlacunar stroke being the major ischemic stroke subtype, increasing the number of people meeting the American Heart Association's goal for ideal and intermediate physical activity criteria may help reduce the stroke burden in the American population through improvement in the known mediators. However, further large cohort studies are needed to verify these results before they can be incorporated into specific practical advice for the general population.

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Disclosure Statement

None.

References

1 Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J: Executive summary: heart disease and stroke statistics – 2010 update: a report from the American Heart Association. Circulation 2010;121: 948–954.

2 O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S: Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376: 112–123.

3 Lee CD, Folsom AR, Blair SN: Physical activity and stroke risk: a meta-analysis. Stroke 2003;34:2475–2481.

4 Oguma Y, Shinoda-Tagawa T: Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. Am J Prev Med 2004;26:407–418.

5 Wendel-Vos GC, Schuit AJ, Feskens EJ, Boshuizen HC, Verschuren WM, Saris WH, Kromhout D: Physical activity and stroke. A meta-analysis of observational data. Int J Epidemiol 2004;33:787–798.

6 Hu FB, Stampfer MJ, Colditz GA, Ascherio A, Rexrode KM, Willett WC, Manson JE: Physical activity and risk of stroke in women. JAMA 2000;283:2961–2967.

7 Hu G, Sarti C, Jousilahti P, Silventoinen K, Barengo NC, Tuomilehto J: Leisure time, occupational, and commuting physical activity and the risk of stroke. Stroke 2005;36:1994–1999.

8 Lee IM, Paffenbarger RS Jr: Physical activity and stroke incidence: the Harvard Alumni Health Study. Stroke 1998;29: 2049–2054.

9 Willey JZ, Moon YP, Paik MC, Boden-Albala B, Sacco RL, Elkind MS: Physical activity and risk of ischemic stroke in the Northern Manhattan Study. Neurology 2009;73:1774–1779.

10 Evenson KR, Rosamond WD, Cai J, Toole JF, Hutchinson RG, Shahar E, Folsom AR: Physical activity and ischemic stroke risk. The Atherosclerosis Risk in Communities Study. Stroke 1999;30:1333–1339.

11 Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H: A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. Stroke 1997;28: 45–52.

12 Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR: Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke 2006;37:2493–2498.

13 The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989; 129:687–702.

14 Baecke JA, Burema J, Frijters JE: A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936–942.

15 Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS: Physical activity and incidence of coronary heart disease in middle-aged women and men. Med Sci Sports Exerc 1997;29:901–909.

16 Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS: Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–S504.

17 Hertogh EM, Monninkhof EM, Schouten EG, Peeters PH, Schuit AJ: Validity of the modified Baecke questionnaire: comparison with energy expenditure according to the doubly labeled water method. Int J Behav Nutr Phys Act 2008;5:30.

18 Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD: Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586–613.

19 The National Survey of Stroke: National institute of neurological and communicative disorders and stroke. Stroke 1981;12:I1–I91.

20 Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E: Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30: 736–743.

21 Crow RS, Prineas RJ, Rautaharju P, Hannan P, Liebson PR: Relation between electrocardiography and echocardiography for left ventricular mass in mild systemic hypertension (results from Treatment of Mild Hypertension Study). Am J Cardiol 1995;75:1233–1238.

22 Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR: Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2003;34:623–631.

23 Sattelmair JR, Kurth T, Buring JE, Lee IM: Physical activity and risk of stroke in women. Stroke 2010;41:1243–1250.

24 Ohira T, Shahar E, Iso H, Chambless LE, Rosamond WD, Sharrett AR, Folsom AR: Carotid artery wall thickness and risk of stroke subtypes: the atherosclerosis risk in communities study. Stroke 2011;42:397–403.

25 Yatsuya H, Yamagishi K, North KE, Brancati FL, Stevens J, Folsom AR: Associations of obesity measures with subtypes of ischemic stroke in the ARIC study. J Epidemiol 2010; 20:347–354.

26 US Department of Health and Human Services: Physical Activity and Health: A Report of the Surgeon General. Washington, Centers for Disease Control and Prevention, 1996.

Supplementary Material

Table S1. Race-specific multivariable adjusted hazard ratios and 95% confidence intervals for physical activity and stroke

	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
African-Americans				
Total stroke				
No. of cases	252	34	21	
Person-years	40,763.7	7,569.9	6,311.0	
Incidence rate *	6.18 (5.46,6.99)	4.49 (3.21,6.29)	3.33 (2.17,5.10)	
Model 1 † #	1	0.76 (0.53,1.10)	0.58 (0.37,0.90)	0.007
Model 2 ‡ #	1	0.84 (0.58,1.21)	0.64 (0.41,1.01)	0.042
Model 3 § #	1	0.89 (0.61,1.28)	0.71 (0.45,1.11)	0.114
Total ischemic stroke				
No. of cases	223	31	14	
Person-years	40,918.4	7,575.1	6,357.9	
Incidence rate *	5.45 (4.78,6.21)	4.09 (2.88,5.82)	2.20 (1.30,3.72)	
Model 1 † #	1	0.77 (0.53,1.13)	0.43 (0.25,0.74)	0.001
Model 2 ‡ #	1	0.86 (0.59,1.26)	0.49 (0.28,0.84)	0.010
Model 3 § #	1	0.91 (0.62,1.33)	0.53 (0.31,0.92)	0.030
Caucasians				
Total stroke				
No. of cases	244	113	76	
Person-years	86,499.8	50,034.1	34,392.2	
Incidence rate *	2.82 (2.49,3.20)	2.26 (1.88,2.72)	2.21 (1.76,2.77)	
Model 1 † #	1	0.79 (0.63,0.99)	0.77 (0.59,1.00)	0.022
Model 2 ‡ #	1	0.83 (0.66,1.04)	0.82 (0.63,1.06)	0.071
Model 3 § #	1	0.88 (0.70,1.11)	0.90 (0.69,1.18)	0.325
Total ischemic stroke				
No. of cases	207	104	69	
Person-years	86,645.2	50,078.8	34,415.4	
Incidence rate *	2.39 (2.08,2.74)	2.08 (1.71,2.52)	2.00 (1.58,2.54)	
Model 1 † #	1	0.85 (0.67,1.08)	0.81 (0.62,1.07)	0.099
Model 2 ‡ #	1	0.89 (0.70,1.13)	0.86 (0.65,1.13)	0.221
Model 3 § #	1	0.96 (0.75,1.21)	0.96 (0.73,1.28)	0.736

* Incidence rate per 1,000 person-years.

† Adjusted for age, sex and race-center.

‡ Adjusted for age, sex, race-center, cigarette-years and education.

§ Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a),fibrinogen, van Willebrand Factor and white blood cell count.

Not adjusted for race.

Table S2. Race-specific multivariable adjusted hazard ratios and 95% confidence intervals for physical activity and ischemic stroke subtypes.

	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
African-Americans				
Lacunar stroke				
No. of cases	67	6	8	
Model 1 [*§]	1	0.50 (0.21,1.16)	0.78 (0.37,1.64)	0.235
Model 2 [†§]	1	0.57 (0.25,1.34)	0.93 (0.44,1.96)	0.512
Model 3 [‡§]	1	0.57 (0.25,1.34)	1.04 (0.49,2.21)	0.667
Cardioembolic stroke				
No. of cases	47	7	2	
Model 1 [*§]	1	0.95 (0.43,2.13)	0.32 (0.08,1.31)	0.137
Model 2 [†§]	1	1.07 (0.48,2.41)	0.36 (0.09,1.50)	0.234
Model 3 [‡§]	1	1.11 (0.49,2.51)	0.36 (0.09,1.49)	0.242
Nonlacunar stroke				
No. of cases	109	18	4	
Model 1 [*§]	1	0.86 (0.51,1.42)	0.24 (0.09,0.65)	0.005
Model 2 [†§]	1	0.94 (0.57,1.57)	0.27 (0.10,0.73)	0.014
Model 3 [‡§]	1	1.02 (0.61,1.71)	0.30 (0.11,0.81)	0.037
Caucasians				
Lacunar stroke				
No. of cases	34	18	11	
Model 1 [*§]	1	0.86 (0.48,1.53)	0.71 (0.36,1.42)	0.320
Model 2 [†§]	1	0.92 (0.52,1.64)	0.79 (0.39,1.58)	0.506
Model 3 [‡§]	1	1.03 (0.57,1.84)	0.97 (0.48,1.97)	0.969
Cardioembolic stroke				
No. of cases	53	23	18	
Model 1 [*§]	1	0.75 (0.46,1.22)	0.84 (0.49,1.44)	0.378
Model 2 [†§]	1	0.77 (0.47,1.26)	0.88 (0.51,1.51)	0.480
Model 3 [‡§]	1	0.83 (0.51,1.37)	0.96 (0.55,1.68)	0.758
Nonlacunar stroke				
No. of cases	120	63	40	
Model 1 [*§]	1	0.90 (0.66,1.22)	0.83 (0.58,1.19)	0.272
Model 2 [†§]	1	0.93 (0.68,1.26)	0.86 (0.60,1.24)	0.406
Model 3 [‡§]	1	0.99 (0.73,1.35)	0.94 (0.65,1.37)	0.779

[*] Adjusted for age, sex and race-center.

[†] Adjusted for age, sex, race-center, cigarette-years and education.

[‡] Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a),fibrinogen, van Willebrand Factor and white blood cell count.

[§] Not adjusted for race.

Table S3. Multivariate adjusted Hazard ratios and 95% confidence intervals for quartiles* of physical activity and total and ischemic stroke

	Sport Score					Leisure Score				
	Q1	Q2	Q3	Q4	P for trend	Q1	Q2	Q3	Q4	P for trend
Total stroke										
No. of cases	247	173	197	123		304	122	200	114	
Person-years	62,091.9	52,870.8	64,135.0	46,473.1		74,553.7	38,938.4	69,255.0	42,823.6	
Incidence rate†	3.98 (3.51,4.51)	3.27 (2.82,3.80)	3.07 (2.67,3.53)	2.65 (2.22,3.16)		4.08 (3.64,4.56)	3.13 (2.62,3.74)	2.89 (2.51,3.32)	2.66 (2.22,3.20)	
Model 1‡	1	0.81 (0.67,0.99)	0.84 (0.70,1.02)	0.76 (0.61,0.96)	0.021	1	0.94 (0.76,1.17)	0.90 (0.75,1.08)	0.86 (0.69,1.07)	0.134
Model 2 §	1	0.81 (0.67,0.98)	0.89 (0.73,1.08)	0.82 (0.66,1.03)	0.117	1	0.99 (0.80,1.23)	0.95 (0.79,1.14)	0.93 (0.75,1.17)	0.479
Model 3 #	1	0.85 (0.70,1.04)	0.93 (0.77,1.13)	0.93 (0.74,1.17)	0.540	1	1.02 (0.82,1.26)	1.00 (0.83,1.21)	1.04 (0.83,1.31)	0.789
Total ischemic stroke										
No. of cases	211	155	167	115		267	107	171	103	
Person-years	62,263.8	52,961.2	64,244.3	46,521.5		74,736.3	39,012.2	69,375.2	42,867.1	
Incidence rate†	3.39 (2.96,3.88)	2.93 (2.50,3.43)	2.60 (2.23,3.03)	2.47 (2.06,2.97)		3.57 (3.17,4.03)	2.74 (2.27,3.31)	2.46 (2.12,2.86)	2.40 (1.98,2.91)	
Model 1‡	1	0.85 (0.69,1.04)	0.83 (0.67,1.02)	0.82 (0.65,1.04)	0.065	1	0.93 (0.74,1.17)	0.87 (0.71,1.06)	0.88 (0.69,1.11)	0.152
Model 2 §	1	0.85 (0.69,1.04)	0.87 (0.71,1.07)	0.89 (0.70,1.12)	0.261	1	0.99 (0.78,1.24)	0.92 (0.75,1.12)	0.95 (0.75,1.21)	0.483
Model 3 #	1	0.89 (0.72,1.10)	0.91 (0.74,1.12)	1.01 (0.79,1.28)	0.848	1	1.01 (0.80,1.27)	0.97 (0.80,1.19)	1.07 (0.85,1.36)	0.762

* Cut-points for the approximated quartiles were 1.75/2.25/3.0 for the sport score and 2.0/2.25/2.75 for the leisure score.

† Incidence rate per 1000 person-years.

‡ Adjusted for age, sex and race-center.

§ Adjusted for age, sex, race-center, cigarette-years and education.

\# Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a),fibrinogen, van Willebrand Factor and white blood cell count.

Table S4. Multivariate adjusted Hazard ratios and 95% confidence intervals for quartiles* of physical activity and ischemic stroke subtypes

	Sports					Leisure				
	Q1	Q2	Q3	Q4	P for trend	Q1	Q2	Q3	Q4	P for trend
Lacunar stroke										
No. of cases	42	41	41	20		70	25	30	19	
Model 1†	1	1.19 (0.77,1.83)	1.19 (0.76,1.84)	0.88 (0.51,1.53)	0.904	1	0.95 (0.60,1.52)	0.69 (0.44,1.07)	0.74 (0.44,1.25)	0.010
Model 2 ‡	1	1.17 (0.76,1.80)	1.28 (0.83,2.00)	1.00 (0.57,1.73)	0.672	1	1.03 (0.65,1.65)	0.75 (0.48,1.17)	0.83 (0.49,1.41)	0.254
Model 3 §	1	1.21 (0.79,1.87)	1.33 (0.86,2.08)	1.16 (0.66,2.02)	0.365	1	1.04 (0.65,1.67)	0.78 (0.50,1.22)	0.93 (0.55,1.59)	0.452
Cardioembolic stroke										
No. of cases	47	41	33	29		60	29	37	24	
Model 1†	1	0.99 (0.65,1.51)	0.73 (0.46,1.14)	0.92 (0.57,1.48)	0.395	1	1.09 (0.69,1.72)	0.79 (0.52,1.21)	0.85 (0.52,1.39)	0.294
Model 2 ‡	1	0.99 (0.65,1.50)	0.76 (0.48,1.20)	0.98 (0.60,1.59)	0.594	1	1.14 (0.73,1.80)	0.83 (0.54,1.27)	0.92 (0.56,1.51)	0.478
Model 3 §	1	1.04 (0.68,1.58)	0.78 (0.49,1.23)	1.11 (0.68,1.81)	0.882	1	1.16 (0.73,1.83)	0.86 (0.56,1.32)	1.05 (0.64,1.73)	0.789
Nonlacunar stroke										
No. of cases	122	73	93	66		137	53	104	60	
Model 1†	1	0.68 (0.51,0.91)	0.75 (0.57,0.99)	0.75 (0.55,1.02)	0.060	1	0.87 (0.63,1.20)	0.98 (0.75,1.28)	0.95 (0.69,1.30)	0.822
Model 2 ‡	1	0.69 (0.51,0.92)	0.79 (0.60,1.04)	0.80 (0.59,1.09)	0.151	1	0.91 (0.66,1.26)	1.03 (0.79,1.34)	1.02 (0.74,1.40)	0.792
Model 3 §	1	0.72 (0.53,0.96)	0.82 (0.62,1.08)	0.91 (0.66,1.24)	0.458	1	0.93 (0.68,1.29)	1.10 (0.84,1.43)	1.14 (0.83,1.57)	0.325

* Cut-points for the approximated quartiles were 1.75/2.25/3.0 for the sport score and 2.0/2.25/2.75 for the leisure score.

† Adjusted for age, sex and race-center.

‡ Adjusted for age, sex, race-center, cigarette-years and education

§ Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a),fibrinogen, van Willebrand Factor and white blood cell count.

4.3 Physical activity is inversely associated with multimorbidity in elderly men: Results from the KORA-Age Augsburg Study

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Physical activity is inversely associated with multimorbidity in elderly men: Results from the KORA-Age Augsburg Study

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ABSTRACT

Objective. Physical activity is suggested to play a key role in the prevention of several chronic diseases. However, data on the association between physical activity and multimorbidity are lacking.

Methods. Using data from 1007 men and women aged 65–94 years who participated in the population-based KORA (Cooperative Health Research in the Region of Augsburg)-Age project conducted in Augsburg/Germany and two adjacent counties in 2008/09, 13 chronic conditions were identified, and physical activity scores were calculated based on the self-reported physical activity scale for the elderly (PASE). Multivariable sex-specific logistic regression was applied to determine the association of the continuous physical activity score with multimorbidity (≥2 out of 13 diseases).

Results. Physical activity (mean PASE score ± SD) was higher in men (125.1 ± 59.2) than in women (112.2 ± 49.2). Among men, the odds ratio (OR) for multimorbidity was 0.73 (95% CI: 0.60–0.90) for a 1 standard deviation increase of the PASE score. No significant results could be observed for women (OR: 1.05; 95% CI: 0.83–1.33).

Conclusion. We demonstrated an inverse association between physical activity and multimorbidity among men. Further prospective studies have to confirm the temporality of effects.

Introduction

Chronic medical conditions such as cardiovascular disease have been identified as the leading cause of morbidity and mortality worldwide (World Health Organization, 2011). With rising life expectancies, multimorbidity, commonly defined as the co-occurrence of two or more chronic diseases in one individual, has reached alarmingly high numbers in the aged population (Marengoni et al., 2011). In a recent study among 123,224 German insurance policy holders aged ≥65 years, prevalence estimates of multimorbidity were 73% (van den Bussche et al., 2011). In the KORA (Cooperative Health Research in the Region of Augsburg)-Age Study, multimorbidity was prevalent in 58.6% of the 4127 persons aged 65–94 years (Kirchberger et al., 2012).

Engaging in an active lifestyle has proven to be protective against chronic diseases, such as coronary heart disease (Hakim et al., 1999) or type 2 diabetes (Hu et al., 2003), as reviewed by Bassuk and Manson (2005). However, epidemiological studies addressing the relationship between physical activity and multimorbidity are lacking and the very few studies investigating this research topic reported conflicting results (Hudon et al., 2008; Kaplan et al., 2001).

The aim of the present study was to investigate whether physical activity assessed as a continuous variable is inversely associated with multimorbidity among a large population-based sample of elderly men and women aged 65–94 years.

Methods

The present data are derived from the KORA-Age Study conducted in 2008/2009, which is a follow-up of all participants aged 65–94 years on December 31st, 2008 (n = 9197), who took part in at least one of the four cross-sectional MONICA (Multinational monitoring of trends and determinants in

Abbreviations: BMI, body mass index; CI, confidence interval; CMD, cardiovascular/metabolic disease; KORA, Cooperative Health Research in the Region of Augsburg; MONICA, Multinational monitoring of trends and determinants in cardiovascular diseases; NCD, non-communicable disease; OR, odds ratio; PASE, Physical activity scale for the elderly; SD, standard deviation.

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cardiovascular diseases)/KORA surveys conducted between 1984 and 2001 in the city of Augsburg and the two adjacent counties. 1079 eligible individuals (response rate: 53.8%) undertook an extensive examination (Kirchberger et al., 2012). After exclusion of persons with missing data (n = 72), the final study sample comprised 506 men and 501 women.

Data on chronic diseases were collected through a self-administered questionnaire mailed to the participants, as well as a standardized telephone interview based on the self-report-generated Charlson Comorbidity Index (Chaudhry et al., 2005). For the present study, multimorbidity was defined as the presence of ≥2 chronic diseases out of a list of 13 chronic diseases (hypertension, eye disease, heart disease, diabetes mellitus, joint disease, lung disease, gastrointestinal disease, mental disease, stroke, cancer, kidney disease, neurological disease, liver disease) (Kirchberger et al., 2012) (Supplementary Tables 1 and 2). In addition, based on a previous study identifying patterns of multimorbidity in the KORA-Age population, the cardiovascular/metabolic disease (CMD) cluster (hypertension, heart disease, diabetes mellitus, stroke, kidney disease) was defined (Kirchberger et al., 2012).

Physical activity was assessed through a standardized face-to-face interview based on the physical activity scale for the elderly (PASE), from which continuous physical activity scores were then calculated (PASE total, leisure and household) (Washburn et al., 1993). Leisure items included questions on light, moderate, vigorous, and endurance exercises, whereas household items incorporated household chores and yard work. Further information on the assessment of covariables can be retrieved from the Supplementary materials.

Baseline characteristics are depicted by means (SD) and relative frequencies. Sex-specific multivariable logistic regression adjusted for age, body mass index (BMI), education, smoking status, alcohol consumption, and nutrition index was used to determine the association between the continuous PASE score for an increase of 1 SD and multimorbidity (1 = yes/0 = no). SAS 9.2 (SAS institute Cary, NC) was used to perform all analyses.

Results

Table 1 shows that the mean PASE Score in any physical activity domain was higher among men than in women. Almost two-thirds of the study population (62.3% of men, 68.5% of women) were multimorbid.

Table 1
Sex-specific percentages and means (SD) of baseline characteristics in the KORA-Age population 2008/09.

	Men	Women
Demographic and lifestyle factors		
No. of subjects	n = 506	n = 501
Age (years)	75.6 (6.4)	75.8 (6.5)
BMI (kg/m^2)	28.4 (3.8)	28.5 (4.7)
Nutrition index	39.1 (5.0)	37.4 (5.4)
Smoker (%)	5.5	3.8
Ex-smoker (%)	56.3	20.0
Never smoker (%)	38.1	76.3
No alcohol consumption (%)	22.3	47.5
Moderate alcohol consumption (%)[a]	61.5	40.7
High alcohol consumption (%)[a]	16.2	11.8
Low education (%)[b]	59.1	86.2
High education (%)[b]	40.9	13.8
Physical activity		
PASE total score	125.1 (59.2)	112.2 (49.2)
PASE leisure score	45.2 (36.8)	37.2 (33.0)
PASE household score	72.0 (37.4)	72.0 (33.8)
Chronic conditions		
Multimorbidity (%)		
≤1 (no)	37.8	31.6
≥2 (yes)	62.3	68.5
Cardiovascular/metabolic cluster (%)		
≤1 (no)	64.8	67.1
≥2 (yes)	35.2	32.9

[a] Alcohol consumption categories: moderate (for men: >0<40 g/day, for women: >0-< 20 g/day), high consumption (for men: ≥40 g/day, for women: ≥20 g/day).
[b] Education categories: low (≤10 years of education), high educational level (≥11 years of education).

Hypertension (62.3%) was the most frequently reported individual condition, followed by eye disease (45.3%), heart disease (30.6%) and joint disease (18.2%). The most common disease pairs were hypertension and eye disease (30.2%), and 6.3% of the study participants indicated that they exclusively suffered from those two chronic diseases. The most frequent combination of three diseases was eye disease, heart disease, and hypertension (11.9%) (data not shown).

Multimorbidity was inversely associated with the total PASE score among men. Furthermore, household and total physical activity were significantly related with the CMD cluster. Among women, no significant results could be observed for any of the investigated PASE scores (Table 2).

Additional analyses of total PASE score quartiles showed that the association with multimorbidity among men was mainly observed in the highest quartile versus the lower ones, whereas among women, no quartile reached statistical significance (Supplementary Fig. 1). Furthermore, the relation between physical activity and single chronic diseases was explored separately (Supplementary Figs. 2 and 3).

Discussion

In this cross-sectional analysis of 1007 elderly participants, our data suggest an inverse association between physical activity and multimorbidity in men, but not in women.

To date, very few population-based studies have been devoted to the topic of multimorbidity and physical activity. In a Canadian study among 12,611 individuals aged 65 years and older (Kaplan et al., 2001), the absence of 13 chronic conditions was related to frequent physical activity. However, results from another study among 16,782 participants aged 18–69 differed and could not report an association between multimorbidity (≥2 out of 17 chronic diseases) and self-reported physical activity (Hudon et al., 2008). Although comparability to these two studies might be somewhat difficult due to different measures of physical activity, the present study supports the findings by Kaplan et al., and provides an even more accurate assessment of physical activity.

The findings from the present study also suggest sex differences in the association between physical activity and multimorbidity. An explanation might be that women tend to overreport medical conditions and disability (Murtagh and Hubert, 2004). Thus, the association among women might have been biased through some misclassification of multimorbidity.

The urgent need for action prompted the United Nations to hold a high level meeting in New York in September 2011, to set up an international agenda for the prevention and control of the major Non-Communicable Diseases (NCD): heart disease, stroke, cancer, diabetes, and chronic respiratory diseases (Beaglehole et al., 2011a). Furthermore, the Lancet NCD Action Group and the NCD Alliance identified physical activity as one of five prevention strategies to counter the negative trend of rising NCDs (Beaglehole et al., 2011b).

Table 2
Adjusted OR (95% CI)[a] of multimorbidity in association with PASE Scores for an increase of 1 SD. Results from the KORA-Age population 2008/09.

	Men	Women
Multimorbidity		
PASE total score	0.73 (0.60–0.90)	1.05 (0.83–1.33)
PASE leisure score	0.85 (0.70–1.03)	0.90 (0.73–1.11)
PASE household score	0.89 (0.73–1.08)	1.16 (0.93–1.45)
CMD cluster		
PASE total score	0.69 (0.56–0.86)	1.02 (0.81–1.28)
PASE leisure score	0.87 (0.71–1.07)	1.02 (0.82–1.27)
PASE household score	0.76 (0.63–0.93)	1.01 (0.82–1.25)

[a] Adjusted for age (cont.), body mass index (cont.), education (low/high), nutrition index (cont.), alcohol consumption (no/moderate/high), and smoking status (smoker/ex-smoker/never smoker).

Yet, despite the well-established adverse health effects of physical inactivity (Lee et al., 2012), engagement in physical activity remains poor in many countries worldwide (Hallal et al., 2012). According to the first results of the nationwide "German Health Interview and Examination Survey for Adults" (DEGS) among 7988 participants aged 18–79 years, physical activity levels have clearly risen in the German population as compared to the last nationwide survey in 1998. However, only 25.4% of men and 15.5% of women reached the minimum activity level of 2.5 h per week, as recommended by the World Health Organization (Kurt, 2012).

Although this study has numerous strengths (population-based design, careful evaluation of risk factors, use of a widely-applied multimorbidity complex, and domain-specific physical activity questionnaire), there are also several limitations which include the self-reported data on physical activity and chronic diseases, which could have led to recall and/or reporting bias. Due to moderate participation rates in the physical examination, selection bias might have occurred. Furthermore, due to the cross-sectional design of the study, the results need to be interpreted with caution, as causal inference cannot be made.

In conclusion, physical activity was inversely associated with multimorbidity among men aged 65–94 years. Further large prospective population-based studies are needed to explore the possible sex differences and to confirm the temporality of the observed relationship. In view of global population aging and the NCD burden that is associated with growing life expectancies around the world, it is imperative to use physical activity as an important dimension of prevention.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2013.02.014.

Conflict of interest statement

None of the authors declare any actual or potential conflict of interest.

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References

Bassuk, S.S., Manson, J.E., 2005. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J. Appl. Physiol. 99, 1193–1204.

Beaglehole, R., Bonita, R., Alleyne, G., et al., 2011a. UN high-level meeting on non-communicable diseases: addressing four questions. Lancet 378, 449–455.

Beaglehole, R., Bonita, R., Horton, R., et al., 2011b. Priority actions for the non-communicable disease crisis. Lancet 377, 1438–1447.

Chaudhry, S., Jin, L., Meltzer, D., 2005. Use of a self-report-generated Charlson Comorbidity Index for predicting mortality. Med. Care 43, 607–615.

Hakim, A.A., Curb, J.D., Petrovitch, H., et al., 1999. Effects of walking on coronary heart disease in elderly men: the Honolulu Heart Program. Circulation 100, 9–13.

Hallal, P.C., Andersen, L.B., Bull, F.C., Guthold, R., Haskell, W., Ekelund, U., 2012. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 380, 247–257.

Hu, G., Qiao, Q., Silventoinen, K., et al., 2003. Occupational, commuting, and leisure-time physical activity in relation to risk for type 2 diabetes in middle-aged Finnish men and women. Diabetologia 46, 322–329.

Hudon, C., Soubhi, H., Fortin, M., 2008. Relationship between multimorbidity and physical activity: secondary analysis from the Quebec health survey. BMC Publ. Health 8, 304.

Kaplan, M.S., Newsom, J.T., McFarland, B.H., Lu, L., 2001. Demographic and psychosocial correlates of physical activity in late life. Am. J. Prev. Med. 21, 306–312.

Kirchberger, I., Meisinger, C., Heier, M., et al., 2012. Patterns of multimorbidity in the aged population. Results from the KORA-Age study. PLoS One 7, e30556.

Kurt, B.-M., 2012. Erste Ergebnisse aus der "Studie zur Gesundheit Erwachsener in Deutschland" (DEGS). Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 55, 980–990.

Lee, I.M., Shiroma, E.J., Lobelo, F., Puska, P., Blair, S.N., Katzmarzyk, P.T., 2012. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 380, 219–229.

Marengoni, A., Angleman, S., Melis, R., et al., 2011. Aging with multimorbidity: a systematic review of the literature. Ageing Res. Rev. 10, 430–439.

Murtagh, K.N., Hubert, H.B., 2004. Gender differences in physical disability among an elderly cohort. Am. J. Public Health 94, 1406–1411.

van den Bussche, H., Koller, D., Kolonko, T., et al., 2011. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Publ. Health 11, 101.

Washburn, R.A., Smith, K.W., Jette, A.M., Janney, C.A., 1993. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J. Clin. Epidemiol. 46, 153–162.

World Health Organization, 2011. Global Status Report On Noncommunicable Diseases 2010. World Health Organization, Geneva, p. ix (164 pp.).

Supplementary material

Supplementary methods section

Height and weight were measured by trained medical staff and body mass index (BMI) was then calculated as weight in kilograms divided by height in meters squared.

Education was dichotomized into low (≤10 years of education) and high educational level (≥11 years of education).

Smoking levels were categorized as follows: current cigarette smokers, ex-smokers and never smokers.

Alcohol consumption was categorized into no, moderate (for men: >0<40 g/day, for women: >0-<20 g/day), and high consumption (for men: ≥40 g/day, for women: ≥20 g/day).

The nutrition index was based on a 12-item healthy diet list about vegetable/fruit consumption and eating habits, ranging from 0 to 48. Questions and weighting points were assessed according to the Seniors in the community: risk evaluation for eating and nutrition, Version II (SCREEN II) questionnaire.[1] A score of <35 was considered an unhealthy diet, a score of ≥35 and <40 was considered a moderately healthy diet, and a score of ≥40 was considered a healthy diet.

According to the norms listed by the New England Research Institutes[2], mean ± SD PASE score in a general population of 222 for men and women aged 65-100 years were as follows:

Men: 144.3 ± 58.6 (65-69 yrs), 102.4 ± 53.7 (70-75 yrs), 101.8 ± 45.7 (76-100 yrs);

Women: 112.7 ± 64.2 (65-69 yrs), 89.1 ± 55.5 (70-75 yrs), 62.3 ± 50.7 (76-100 yrs).

The present study was approved by the local authorities and all subjects provided a written informed consent.

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[1] Keller HH, Goy R, Kane SL. Validity and reliability of SCREEN II (Seniors in the community: risk evaluation for eating and nutrition, Version II). Eur J Clin Nutr 2005;59(10):1149-57.

[2] New England Research Institutes, Inc. PASE Physical Activity Scale for the Elderly. Administration and Scoring Instruction Manual. 1991; Watertown, MA.

Supplementary Tables

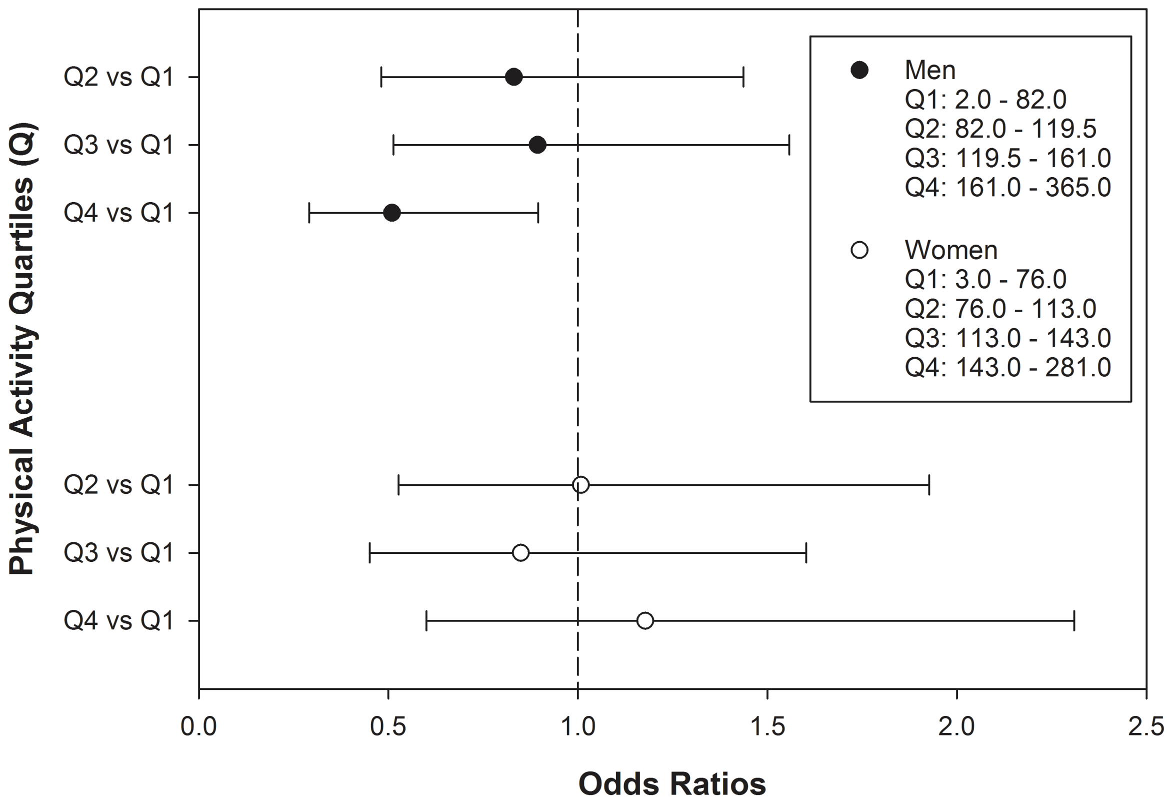
Supplementary Table 1. Chronic conditions collected by telephone interview within the KORA-Age project, 2008-2009.

Disease group	Information on the diseases covered
Heart disease	Angina, cardiac insufficiency, coronary heart disease
Kidney disease	Kidney
Joint disease	Arthritis, rheumatism
Lung disease	Asthma, emphysema, chronic obstructive pulmonary disease
Gastrointestinal disease	Stomach/duodenal ulcer, colitis, gallbladder infection
Neurologic disease	Multiple sclerosis, Parkinson's disease, epilepsy
Liver disease	Cirrhosis
Eye disease	Glaucoma, cataract, macular degeneration, diabetic retnopathy, retinitis pigmentosa
Depression	Assessed by the Geriatric Depression Scale
Anxiety	Assessed by the Generalized Anxiety Disorder Scale-7

Supplementary Table 2. Chronic conditions collected by questionnaire within the KORA-Age project, 2008-2009.

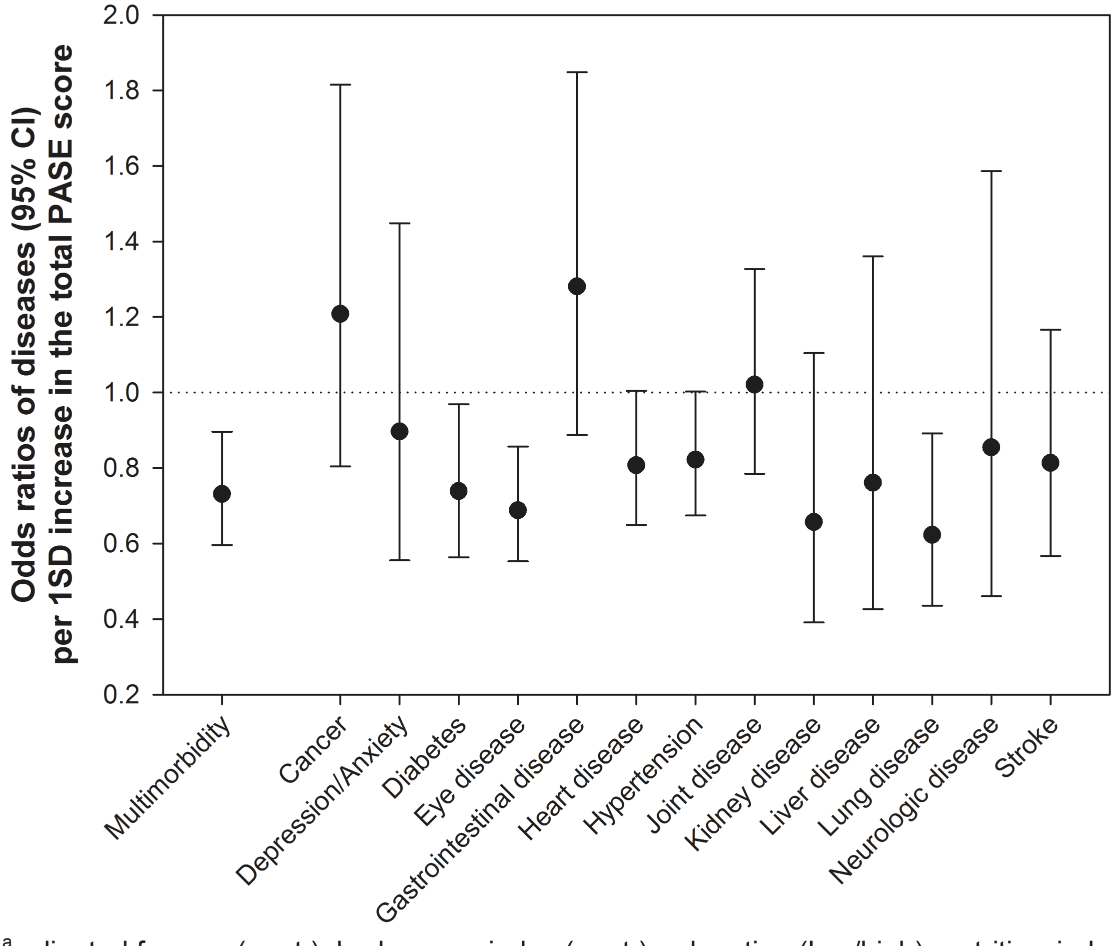
Disease group	Information on the diseases covered
Hypertension	Hypertension
Myocardial infarction	Follow-up questions: number of MIs, year, and hospital
Stroke	Follow-up questions: number of strokes, year, and hospital
Diabetes mellitus	Follow-up questions: year, current treatment
Cancer	All cancer types

Supplementary Figure 1: Odds ratios[a] of multimorbidity according to total PASE quartiles



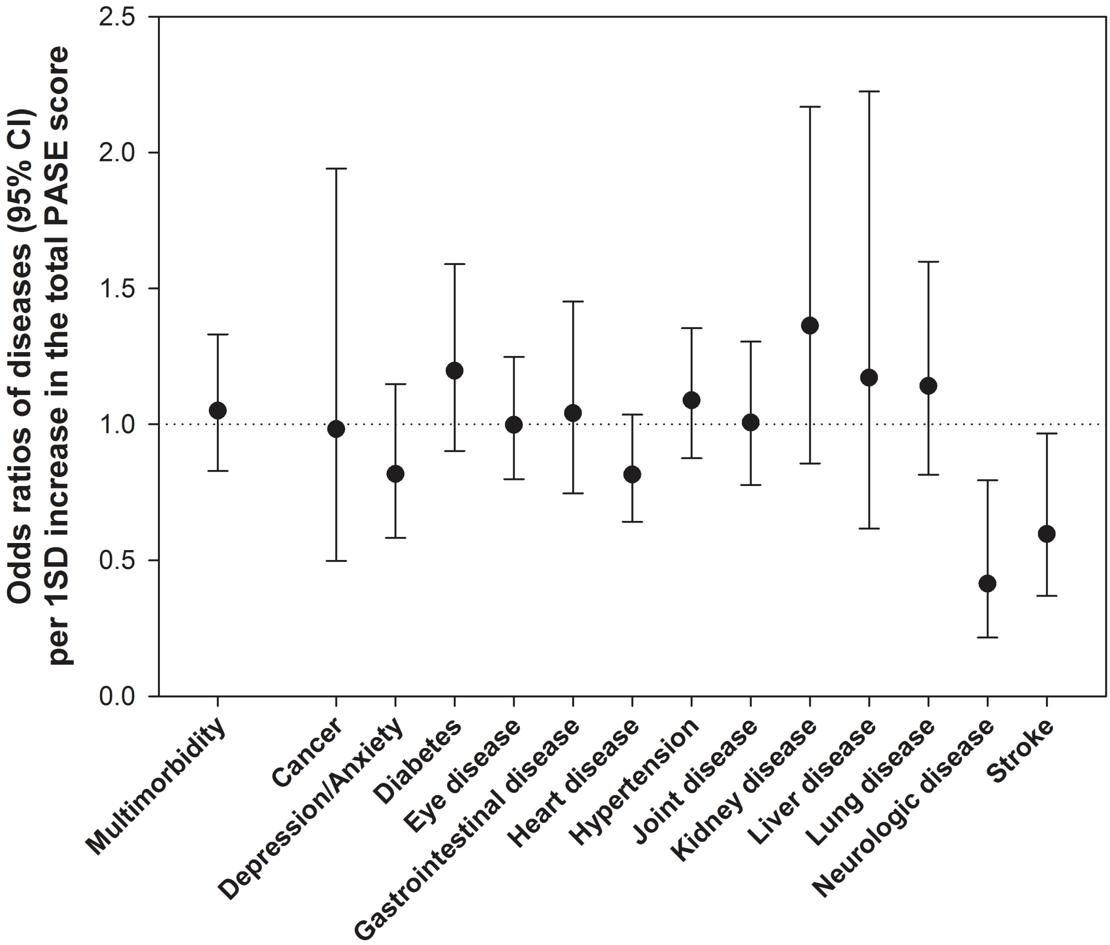
[a] adjusted for age (cont.), body mass index (cont.), education (low/high), nutrition index (cont.), alcohol consumption (no/moderate/high), and smoking status (smoker/ex-smoker/ never smoker).

Supplementary Figure 2: Association[a] between total physical activity and both multimorbidity and single chronic diseases among men.



[a] adjusted for age (cont.), body mass index (cont.), education (low/high), nutrition index (cont.), alcohol consumption (no/moderate/high), and smoking status (smoker/ex-smoker/ never smoker).

Supplementary Figure 3: Association[a] between total physical activity and both multimorbidity and single chronic diseases among women.



[a] adjusted for age (cont.), body mass index (cont.), education (low/high), nutrition index (cont.), alcohol consumption (no/moderate/high), and smoking status (smoker/ex-smoker/ never smoker).

4.4 Association between domains of physical activity and all-cause, cardiovascular and cancer mortality

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MORTALITY

Association between domains of physical activity and all-cause, cardiovascular and cancer mortality

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Abstract Few studies have investigated the independent effects of domain-specific physical activity on mortality. We sought to investigate the association of physical activity performed in different domains of daily living on all-cause, cardiovascular (CVD) and cancer mortality. Using a prospective cohort design, 4,672 men and women, aged 25–74 years, who participated in the baseline examination of the MONICA/KORA Augsburg Survey 1989/1990 were classified according to their activity level (no, light, moderate, vigorous). Domains of self-reported physical activity (work, transportation, household, leisure time) and total activity were assessed by the validated MOSPA (MONICA Optional Study on Physical Activity) questionnaire. After a median follow-up of 17.8 years, a total of 995 deaths occurred, with 452 from CVD and 326 from cancer. For all-cause mortality, hazard ratios and 95% confidence interval (HR, 95% CI) of the highly active versus the inactive reference group were 0.69 (0.48–1.00) for work, 0.48 (0.36–0.65) for leisure time, and 0.73 (0.59–0.90) for total activity after multivariable adjustments. Reduced risks of CVD mortality were observed for high levels of work (0.54, 0.31–0.93), household (0.80, 0.54–1.19), leisure time (0.50, 0.31–0.79) and total activity (0.75, 0.55–1.03). Leisure time (0.36, 0.23–0.59) and total activity (0.62, 0.43–0.88) were associated with reduced risks of cancer mortality. Light household activity was related to lower all-cause (0.82, 0.71–0.95) and CVD (0.72, 0.58–0.89) mortality. No clear effects were found for transportation activities. Our findings suggest that work, household, leisure time and total physical activity, but not transportation activity, may protect from premature mortality.

Keywords Domains of physical activity · Exercise · Health-promoting effects · Mortality

Abbreviations

95% CI	95% Confidence Interval
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
CVD	Cardiovascular Disease
HDL	High-density Lipoprotein Cholesterol
HR	Hazard Ratio
ICD	International Classification of Diseases
MET(s)	Metabolic Equivalent(s)
MONICA/KORA	Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Augsburg
MOSPA	MONICA Optional Study on Physical Activity

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Introduction

The health-promoting effects of regular physical activity on cardiovascular disease (CVD), chronic morbidity and premature death are well-established [1–3]. Despite the knowledge of its health-enhancing effects, engagement in exercise, especially in industrialized societies, remains poor across many European countries [4]. In recent years, efforts have been made to counter the increasing physically inactive lifestyle of many individuals through campaigns, on both national and international levels (e.g. by Federal Ministries of Health or the World Health Organization), to incorporate physical activity into daily living. Recent recommendations advocate a minimum of 30 min of at least moderate-intensity activities on most days of the week [5]. Although the association between physical activity and mortality has been examined extensively in the past several years [6–8], few studies have focused on domain-specific activities performed during daily routines [9–11]. Specifically, analyses of the four most common domains (domestic, transportation, work, leisure time) of physical activity on mortality are sparse [12]. For people not willing or not able to engage in leisure time activities at all, information on the effects of physical activity beyond leisure time is crucial. The importance of incorporating regular activities into daily routines has been averred by several physical activity experts in their recommendations, suggesting a protective effect from premature morbidity and mortality [13, 14]. Especially household physical activity in relation to mortality has not been given sufficient attention; the distinct effect of regular housework in terms of all-cause and CVD mortality has only recently been investigated [12, 15]. In addition, few population-based data exist on different types and intensities of activity undertaken during daily routines and their relation to cause-specific mortality [11, 16, 17]. These considerations, and the insufficient prior systematic investigation of physical activity, subdivided into different domains, on all-cause, CVD and cancer mortality in a population-based cohort, were the motivation for this study.

Methods

Study population

The presented data were derived from the second MONICA/KORA Augsburg survey (S2), conducted in 1989/1990 in the city of Augsburg and two adjacent counties. The study design, sampling, and data collection have been described in detail elsewhere [18, 19]. In brief, for S2, 6,637 individuals were drawn from a target population of 349,050 residents aged 25–74 years, using two-stage random sampling stratified by age and sex. Of those, 4,940 individuals participated in the baseline survey (baseline response: 76.9%). All subjects are currently followed within the framework of the Cooperative Health Research in the Region of Augsburg (KORA). Individuals with incomplete data on outcome (mortality, $n = 6$), exposure (physical activity, ($n = 26$)), or co-variables ($n = 268$), were sequentially excluded from further analyses. Thus, 4,672 participants (2,373 men and 2,299 women) were available for the final analyses. The study was approved by the local authorities and all subjects provided a written informed consent.

Baseline measurements

MONICA optional study on physical activity

The MOSPA questionnaire was designed to assess different domains of physical activity, asking participants to report the time usually spent on being physically active during work, transportation (walking or biking), household and/or leisure time, during a normal week over the past year. Based upon the subjects' indications, metabolic equivalents (METs, expressed in minutes per week) were calculated by means of a standardized program derived from the Compendium of Physical Activities [20] and provided by the Centers for Disease Control and Prevention (CDC). Following the recommendations of the CDC and the American College of Sports Medicine [21], intensity categories (no, light, moderate, vigorous) were defined for each physical activity domain. Individuals were graded into the category according to the highest intensity level of their activities. For instance, subjects who engaged in light and moderate physical activity were categorized as moderately active, whereas cohort members who reported light and vigorous activity were classified in the highest activity level. A minimum time spent while executing the level of physical activity in each category was determined a priori. Thus, the four activity levels can be characterized as follows:

Participants who are represented in the category "*no physical activity*" did not report any light, moderate or vigorous activity in the respective domain of physical activity. "*Light physical activity*" was defined as activities causing no or little increase in breathing or heart rate (<3.0 METs). "*Moderate physical activity*" was defined as activities causing little to moderate rise in breathing and heart rate (3.0–6.0 METs). Participants below the cut-off point of 120 min per week spent on moderate physical activity were reassigned to light physical activity. The highest activity level, "*vigorous physical activity*", classifies persons who engage in activities causing moderate to large increase in breathing and heart rate (>6.0 METs).

Participants below the cut-off point of 90 min per week were reassigned to moderate physical activity.

The MET-minutes per week of the four domains of physical activity were then summed up, thereby creating a fifth rubric (total physical activity) that represents the overall activity level in the study participants. Thirty-six persons who stated no physical activity at all, in any of the four physical activity domains, were allotted to "no physical activity" in each single domain, but were assigned to "light physical activity" for the total activity, in order to avoid a reference group of only thirty-six subjects.

After restricting the analyses of occupational activity to employed participants only, data from 2,538 cohort members were available for further analyses of work physical activity. With considerations for the activity levels reported in our population, we amended the MOSPA questionnaire to include the following categories for the activity domain variables; four activity levels for transportation and leisure time (no, light, moderate, vigorous), three for household (no, light, moderate) and total (light, moderate vigorous), and two for work activity (light, moderate).

Outcome definition

End points used in this study were all-cause mortality and mortality from any CVD, cancer or other causes that occurred until December 31st, 2007. Deaths were ascertained by regularly checking the vital status of all sampled persons of the MONICA survey through the population registries inside and outside the study area. Death certificates were obtained from local health authorities. Using the 9th revision of the International Classification of Diseases (ICD), death certificates were coded for the underlying cause of death. Until December 31st, 2007, 995 subjects died from all-cause mortality (ICD-9: 001-999), 452 from CVD (ICD-9: 390-459), and 326 from cancer (ICD-9: 140-208). Twenty individuals were lost to follow-up in the final dataset.

Covariables

Baseline information on socio-demographic factors, medical history, and lifestyle habits were gathered by trained medical staff during a standardized interview. Educational attainment was estimated by recording years of school completed and then dichotomized into low ($\leq$11 years of school) and high educational level ($\geq$12 years of school).

Assessment of alcohol intake (in grams per day) was based on data regarding weekday and weekend consumption of beer, wine, and spirits and categorized into no, moderate (for men: >0 to <40 g/day, for women: >0 to <20 g/day) and high alcohol consumption (for men: $\geq$40 g/day, for women: $\geq$20 g/day). Study participants provided information about whether they had ever smoked cigarettes regularly (current, past, never).

Blood pressure (BP) and body mass index (BMI) were measured by trained medical staff. BMI was calculated as weight in kilograms divided by height in square meters. BP was measured with a Hawksley Random Zero sphygmomanometer. Three BP recordings were taken from each individual after completion of the interview, i.e. after being at rest in a sitting position for an average of 30 min. The BP results provided are based on the mean of the second and third BP recordings. Further details on the measurement procedures are reported elsewhere [22]. Actual hypertension was defined as blood pressure values $\geq$140/90 mmHg and/or the usage of antihypertensive medication, given that the subjects were aware that they had hypertension [22].

Nonfasting blood samples were collected from all subjects under standardized conditions in 1989/1990 [23]. Total cholesterol was measured by an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany) and high-density lipoprotein (HDL) cholesterol was measured after precipitation with phosphotungstic acid/Mg2+ (Boehringer Mannheim, Mannheim, Germany) on fresh samples.

Statistical analyses

Baseline characteristics are presented by means and standard deviations for continuous variables. Categorical variables are expressed as relative frequencies. Pearson correlation was computed to determine the relationships between the continuous variables of interest. To avoid multicollinearity, only BMI was used for further analyses, as waist circumference was highly correlated with BMI ($r = 0.79$).

Cox proportional hazards models, with days as the timescale, were applied to compute the hazard ratios and 95% confidence intervals (HR, 95% CI) for all-cause, CVD, and cancer mortality. The proportional hazards assumption was tested by the inspection of log((-log)event) versus log of event times and proved to be sufficient. Persons categorized in "no physical activity" were defined as the reference group in each physical activity domain, except for work and total activity, in which light physical activity served as the comparison group. To take the non-linear increase of death risk with age into account, stratification by age groups (25–49, 50–59, 60–69, 70–74 years) was included in the Cox models. For each of the four physical activity domains, we calculated HR adjusted for sex, BMI, systolic blood pressure, total-to-HDL cholesterol ratio, education, smoking status, alcohol consumption, myocardial infarction, stroke, diabetes, cancer, self-reported limited physical activity due to health problems and the remaining other domains of physical activity. For total activity, the same model was calculated, but no adjustments for other domains of physical activity were made.

To assess the a priori assumed dose–response relation between domain-specific physical activity and type of mortality, linear trend tests across physical activity levels were performed by entering the categorical activity variable as a continuous variable into the Cox model. Effect modifications were tested between physical activity and sex, as well as selected covariates, on mortality by additionally entering an interaction term of the respective variables into the model.

Due to the identified interactions, we then examined the joint effects of leisure time activity and systolic BP, as well as leisure time activity and BMI on all-cause mortality.

Tests were considered statistically significant with a two-sided $P < 0.05$. The statistical software package SAS 9.1.3 (SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses.

Results

Between 1989 and 2007 (median follow-up period 17.8 years), 995 participants died; 452 from CVD and 326 from cancer. Baseline information of the study sample is presented in Table 1. Participants can be described as middle-aged and mostly free of chronic conditions. One-fifth of the subjects died during the 17.8 years of follow-up.

With regard to total and work activity, the majority of both men and women were moderately active, whereas during leisure time, light activities were most frequently reported. Different activity patterns for men and women were observed for transportation activity, in which most men reported no activity and women mainly engaged in moderate activities. This was similar in the household domain, whereby most men reported no activity and light intensity activities predominate among women.

As shown in Table 2, significant risk reductions for all-cause and CVD mortality can be reported for work, household, leisure time (only all-cause) and total physical activity ($P_{trend} < 0.05$). Engagement in leisure time and total activity was inversely associated with cancer mortality ($P_{trend} < 0.01$).

Being moderately active at work compared to the light activity group significantly reduced the risk for all-cause (HR = 0.69; 95% CI, 0.48–1.00) and CVD mortality (HR = 0.54; 95% CI, 0.31–0.93). For the household domain, significant risk reductions were only observed in light activities (all-cause mortality: HR = 0.82; 95% CI, 0.71–0.95; CVD mortality: HR = 0.72; 95% CI, 0.58–0.89). Compared to being sedentary, being vigorously active during leisure time significantly reduced the risk for all-cause (HR = 0.48; 95% CI, 0.36–0.65) and CVD mortality (HR = 0.50; 95% CI, 0.31–0.79). However, neither moderate nor light activities during leisure time were associated with a significantly decreased CVD mortality risk. Participants engaging in vigorous leisure activity substantially lowered their risk of cancer mortality (HR = 0.36; 95% CI, 0.23–0.59). The remarkable decrease in cancer mortality associated with leisure time physical activity is actually already present in light (HR = 0.58; 95% CI, 0.42–0.80) and moderately (HR = 0.56; 95% CI, 0.40–0.77) active subjects. For total activity, subjects categorized in vigorous activities were at reduced risk for all-cause (HR = 0.73; 95% CI, 0.59–0.90) and cancer mortality (HR = 0.62; 95% CI, 0.43–0.88). With regard to CVD mortality, a significant trend was observed, but the individual HR did not reach significance.

For transportation activity, however, no significant results or clear trends can be noted for either all-cause, CVD, or cancer mortality.

We also calculated the Cox model with each activity domain entered individually into the multivariable-adjusted model. Almost no statistical differences were observed, indicating that the domains are, in fact, independent of each other. In addition, the above-mentioned results in the fully adjusted model did not change after excluding those persons who died during the first 2 years of follow-up ($n = 55$, data not shown). Because the relationship between mortality and physical activity was not altered by sex, except for CVD mortality and transportation activity ($P = 0.049$), when examining the interactions in any combination, all analyses were performed using combined data with both men and women (range of the P-values across all activity domains: 0.133–0.846 for all-cause, 0.190–0.886 for CVD and 0.058–0.834 for cancer mortality).

Both systolic BP ($P = 0.030$) and BMI ($P = 0.023$) showed a significant interaction with leisure time physical activity on all-cause mortality. We therefore assessed the joint effects of systolic BP as well as BMI and different levels of leisure time activity. Persons engaging in vigorous leisure activity, in combination with a systolic BP < 140 mm Hg (Fig. 1) and a BMI < 30 (Fig. 2), respectively, served as reference groups.

As shown in Fig. 1, the effect of increasing activity levels during leisure time was stronger among participants with a systolic BP ≥ 140 mm Hg in reducing all-cause mortality. Compared with the reference group, inactive persons with an increased systolic BP had the highest mortality risk (HR = 2.10; 95% CI, 1.36–3.24) in our sample ($P < 0.001$). We recalculated the same model, in which we additionally considered antihypertensive medication, but the results were very similar (data not shown).

Figure 2 demonstrates a different pattern; the highest risk of mortality was found in inactive subjects with a BMI < 30 (HR = 2.46; 95% CI, 1.76–3.43) compared to the reference group ($P < 0.001$). On the contrary, mortality

Table 1 Baseline characteristics

	Men ($n = 2{,}372$)	Women ($n = 2{,}299$)	Total ($n = 4{,}672$)
Personal characteristics			
Age (years)[a]	49.8 (14.2)	49.4 (13.8)	49.6 (14.0)
BMI (kg/m^2)[a]	27.1 (3.6)	26.3 (4.8)	26.7 (4.3)
Total-to-HDL-cholesterol ratio[a]	5.1 (2.2)	4.0 (1.5)	4.5 (1.9)
Systolic blood pressure (mm Hg)[a]	135.6 (17.5)	129.2 (20.0)	132.4 (19.0)
Diastolic blood pressure (mm Hg)[a]	81.8 (11.1)	77.9 (10.8)	79.9 (11.1)
Actual hypertension (%)	46.0	33.3	39.7
Low educational level (%)	67.3	81.9	74.5
No alcohol consumption (%)	18.6	44.7	31.5
Moderate alcohol consumption (%)	50.1	36.9	43.6
High alcohol consumption (%)	31.3	18.4	24.9
Current smoker (%)	30.5	21.3	26.0
Ex-smoker (%)	39.8	16.7	28.4
Never smoker (%)	29.7	62.0	45.6
Self-reported limited physical activity due to health problems (%)	26.7	23.4	25.1
Chronic conditions			
Diabetes (%)	5.3	4.0	4.7
Myocardial infarction (%)	3.9	0.8	2.4
Stroke (%)	1.5	0.8	1.2
Cancer (%)	1.3	1.5	1.4
Physical activity			
Total			
Light (%)	7.1	10.3	8.7
Moderate (%)	56.6	57.5	57.0
Vigorous (%)	36.2	32.2	34.2
Work[b]			
Light (%)	6.7	7.3	7.0
Moderate (%)	60.2	34.0	47.3
Transportation			
No (%)	41.9	27.8	35.0
Light (%)	11.9	8.8	10.4
Moderate (%)	27.6	38.1	32.8
Vigorous (%)	18.5	25.3	21.9
Household			
No (%)	61.6	14.0	38.2
Light (%)	36.3	74.8	55.3
Moderate (%)	2.1	11.1	6.5
Leisure time			
No (%)	8.9	11.1	10.0
Light (%)	38.3	43.8	41.1
Moderate (%)	30.5	35.2	32.8
Vigorous (%)	22.3	9.8	16.2
Deaths			
All-cause (%)	26.8	15.7	21.3
CVD (%)	12.3	7.0	9.7
Cancer (%)	8.3	5.6	7.0

[a] Values are presented as mean (SD)

[b] Unemployed subjects ($n = 2{,}134$; 45.7%) were excluded

Table 2 Hazard Ratios (HR) by domain and physical activity level for all-cause, CVD and cancer mortality

	All-cause, 995 events			CVD, 452 events		Cancer, 326 events	
	No. of subjects	No. of deaths	HR[a] (95% CI)	No. of deaths	HR[a] (95% CI)	No. of deaths	HR[a] (95% CI)
Work[b]							
Light	328	36	Reference	17	Reference	13	Reference
Moderate	2,210	198	0.69 (0.48–1.00)	75	0.54 (0.31–0.93)	78	0.84 (0.46–1.54)
			$P = 0.048$		$P = 0.028$		$P = 0.574$
Transportation							
No	1,633	333	Reference	145	Reference	108	Reference
Light	485	86	1.08 (0.85–1.37)	31	0.94 (0.63–1.39)	40	1.49 (1.03–2.15)
Moderate	1,533	374	1.16 (1.00−1.35)	180	1.23 (0.98–1.55)	121	1.19 (0.91–1.56)
Vigorous	1,021	202	0.95 (0.80–1.14)	96	1.02 (0.78–1.34)	57	0.89 (0.64–1.24)
			$P_{trend} = 0.774$		$P_{trend} = 0.395$		$P_{trend} = 0.836$
Household							
No	1,785	502	Reference	242	Reference	153	Reference
Light	2,582	418	0.82 (0.71–0.95)	174	0.72 (0.58–0.89)	153	0.95 (0.74–1.22)
Moderate	305	75	0.90 (0.69–1.18)	36	0.80 (0.54–1.19)	20	0.90 (0.54–1.49)
			$P_{trend} = 0.043$		$P_{trend} = 0.017$		$P_{trend} = 0.607$
Leisure time							
No	466	137	Reference	53	Reference	57	Reference
Light	1,918	406	0.73 (0.60–0.89)	182	0.81 (0.59–1.11)	135	0.58 (0.42–0.80)
Moderate	1,533	374	0.78 (0.64–0.95)	187	0.97 (0.71–1.33)	108	0.56 (0.40–0.77)
Vigorous	755	78	0.48 (0.36–0.65)	30	0.50 (0.31-0.79)	26	0.36 (0.23–0.59)
			$P_{trend} < 0.001$		$P_{trend} = 0.145$		$P_{trend} < 0.001$
Total							
Light	407	143	Reference	61	Reference	52	Reference
Moderate	2,665	593	0.91 (0.76–1.10)	278	0.98 (0.74–1.30)	193	0.81 (0.60–1.11)
Vigorous	1,600	259	0.73 (0.59–0.90)	113	0.75 (0.55–1.03)	81	0.62 (0.43–0.88)
			$P_{trend} = 0.001$		$P_{trend} = 0.030$		$P_{trend} = 0.005$

[a] Adjusted for sex, BMI, systolic blood pressure, total-to-HDL cholesterol ratio, education, smoking status, alcohol consumption, myocardial infarction, stroke, diabetes, cancer, self-reported limited physical activity due to health problems, and other domains of physical activity. No adjustments for other types of physical activity in total activity

[b] Analyses restricted to working participants ($n = 2{,}538$)

risk does not decrease with increasing level of physical activity within obese cohort members [HR = 2.18 (95% CI, 1.45–3.28) for no, HR = 1.86 (95% CI, 1.38–2.52) for light and moderate, and HR = 2.09 (95% CI, 1.26–3.45) for vigorous leisure physical activity].

Discussion

In our population-based prospective cohort study among middle-aged men and women, work, household, leisure time and total physical activity were significantly associated with a reduced risk of all-cause and CVD (except for leisure activity) mortality. The inverse relationship between leisure time as well as total activity with cancer mortality was highly significant, whereas walking and cycling for transportation was associated with neither all-cause nor cause-specific mortality.

To our knowledge, only one previous European study has individually examined the four most common physical activity domains (domestic, transportation, work, sports/exercise) on mortality, and reported similar results. In addition to total and sports/exercise activities being inversely associated with all-cause and CVD mortality, the authors also found evidence for the benefits of domestic activities, but none for work and transportation-related physical activity [12]. Two other studies have investigated several different forms of physical activity independently in relation to all-cause mortality [9, 11]. With regard to the beneficial impact of leisure time physical activity or total activity, our results are consistent with a previous study which showed a dose–response relationship, predominantly

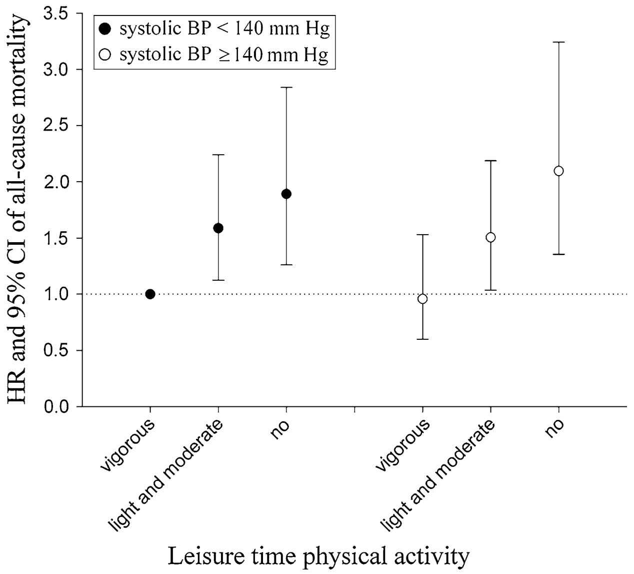

Fig. 1 Hazard Ratios (HR) of all-cause mortality according to the joint effects of leisure time physical activity and systolic BP. Adjusted for sex, BMI, total-to-HDL cholesterol ratio, education, smoking status, alcohol consumption, myocardial infarction, stroke, diabetes, cancer, self-reported limited physical activity due to health problems and other domains of physical activity. $P = 0.030$ for interaction between leisure time physical activity and systolic BP

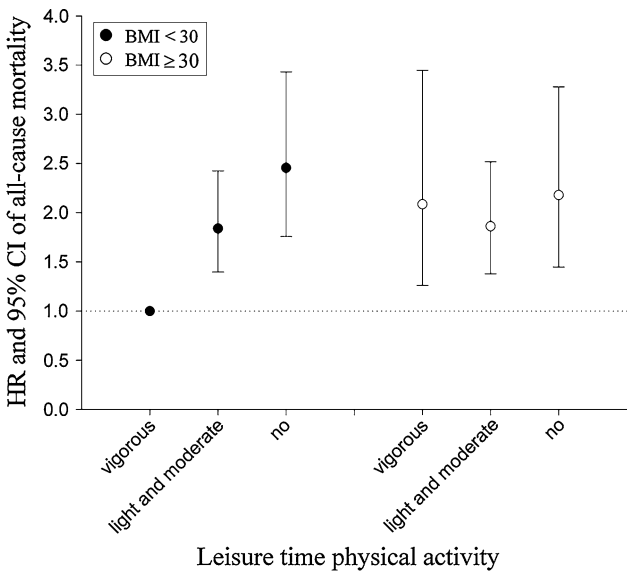

Fig. 2 Hazard Ratios (HR) of all-cause mortality according to the joint effects of leisure time physical activity and BMI. Adjusted for sex, systolic blood pressure, total-to-HDL cholesterol ratio, education, smoking status, alcohol consumption, myocardial infarction, stroke, diabetes, cancer, self-reported limited physical activity due to health problems and other domains of physical activity. $P = 0.023$ for interaction between leisure time physical activity and BMI

in the leisure time domain, with all-cause mortality [24]. In contrast, the significant results for walking or biking as a means of transportation detected by Andersen et al. [9] and Matthews et al. [11] were not observed in the present study which may be explained by the use of different instruments.

In our study, among all three types of mortality investigated, the greatest risk reductions through engagement in leisure time activities are found for overall cancer mortality. Some population studies and reviews detected a reduced risk of cancer mortality through enhanced physical activity among men [25], women [11] or both sexes [16, 17, 26, 27], but none of them has independently examined work, transportation, household and leisure time physical activity. A large prospective follow-up study from Finland [16] reported a significantly lower risk of cancer mortality for both men and women, when comparing high versus low occupational and leisure time physical activity. With regard to our study sample, moderately active individuals almost halved their risk of premature deaths due to cancer, while vigorously active persons further reduced their risk. Likewise, a recent study among 2,560 men investigating the intensity level needed to reduce cancer mortality concluded that people have to engage in at least moderate leisure (sports, exercise) activities (>4.5 METs) to benefit from its effects [28]. Notably, in our population, even light leisure activities (<3.0 METs) offer a substantial risk reduction compared to the inactive reference group. Our findings emphasize the necessity to engage in sports activities and suggest that physical activity in daily routines (e.g. transportation and household activities) do not seem to be sufficient in the prevention of cancer mortality.

The results regarding the interactions of leisure time physical activity with systolic BP and BMI, merit some comment. Subjects who reported to be inactive, had a considerably higher risk of all-cause mortality than participants engaging in vigorous activities in both the systolic BP < 140 mm Hg and the systolic BP ≥ 140 mm Hg group. Men and women with an increased systolic BP seem to benefit slightly more from enhanced leisure time in contrast to those with a normal systolic BP. These findings are in accordance with other studies reporting that high levels of physical activity or aerobic exercise may protect against the adverse effects of elevated systolic BP [29, 30].

Previous studies have hypothesized that high physical activity may attenuate the increased risk of mortality that is related to adiposity [16, 31]. In our population sample, the beneficial effects of physical activity on mortality seem to be present in non-obese men and women (BMI < 30) only.

The strengths of our study include a long follow-up period and its population-based representative design, while including a wide age range. The careful evaluation of important covariates in the MONICA/KORA Augsburg survey at baseline allowed for the adjustment of the most common risk factors related to all-cause, CVD and cancer mortality. Furthermore, data on the concurrent assessment of the four most important domains of physical activity is sparse in the literature, with the majority of previous studies focusing on leisure and/or work-related physical activity [24, 32]. Besides these strengths, the study has also some limitations that need to be considered. As our data on physical activity were self-reported, reporting bias cannot be fully avoided. However, we used a validated and widely-applied questionnaire [33, 34]. Another limitation is that physical activity was only recorded at baseline, making it impossible to report changes of activity patterns over time. We do not have follow-up data on physical activity at an individual level; therefore, we must assume that physical activity patterns remain fairly stable over time. This is a general problem in epidemiological studies and previous studies have also addressed this matter in their limitations [10, 12, 16]. Further research is needed to consider subsequent modifications in physical activity patterns during lifetime. The stringent categorization into low, moderate and vigorous physical activity may have led to misclassification, in some cases. Regardless, this solution worked best to combine the multiple answer options in the MOSPA questionnaire (e.g. subjects engaged in moderate and vigorous physical activity were categorized as vigorously active) and our division most probably reflects the participants' activity level correctly. We do not have data on other transportation-related exposures and participants who frequently walk or bike close to heavily travelled roads may be exposed to hazardous substances such as diesel exhausts and other fumes, which may counterbalance the positive effects of physical activity.

In conclusion, the physical activity domains work, household and leisure time as well as total activity showed inverse associations with mortality. The benefits of physical activity in terms of lower all-cause mortality were greatest among non-obese participants and those with an increased systolic BP. In light of the positive health effects ascribed to regular exercise, it is highly important to disentangle the different forms of physical activity, in order to promote those domains that contribute the most to positive health outcomes. It is therefore important that public health agencies endorse physical activity campaigns of any kind.

Non-exercise activities such as housework or work physical activity should be fully integrated into daily routines as their preventive nature has been proven in previous studies on various health outcomes. The findings of this study specifically underline that engagement in non-exercise activities beyond leisure time physical activity may be conducive to successfully reduce all-cause, CVD and cancer mortality risk.

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References

1. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239–46.
2. U.S. Department of Health and Human Services. Physical activity and health: A report of the surgeon general. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.
3. Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. Sports Med. 2001;31(2):101–14.
4. Sjöström M, Oja P, Hagströmer M, Smith BJ, Bauman A. Health-enhancing physical activity across European Union countries: the Eurobarometer study. J Public Health. 2006;14(5):291–300.
5. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(8):1423–34.
6. Arrieta A, Russell LB. Effects of leisure and non-leisure physical activity on mortality in U.S. adults over two decades. Ann Epidemiol. 2008;18(12):889–95.
7. Dorn JP, Cerny FJ, Epstein LH, Naughton J, Vena JE, Winkelstein W Jr, et al. Work and leisure time physical activity and mortality in men and women from a general population sample. Ann Epidemiol. 1999;9(6):366–73.
8. Mensink GB, Deketh M, Mul MD, Schuit AJ, Hoffmeister H. Physical activity and its association with cardiovascular risk factors and mortality. Epidemiology. 1996;7(4):391–7.
9. Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. Arch Intern Med. 2000;160(11):1621–8.
10. Barengo NC, Hu G, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. Eur Heart J. 2004;25(24):2204–11.
11. Matthews CE, Jurj AL, Shu XO, Li HL, Yang G, Li Q, et al. Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. Am J Epidemiol. 2007;165(12):1343–50.
12. Besson H, Ekelund U, Brage S, Luben R, Bingham S, Khaw KT, et al. Relationship between subdomains of total physical activity and mortality. Med Sci Sports Exerc. 2008;40(11):1909–15.
13. Dunn AL, Andersen RE, Jakicic JM. Lifestyle physical activity interventions. History, short- and long-term effects, and recommendations. Am J Prev Med. 1998;15(4):398–412.

14. Murphy M. Lifestyle physical activity for health In: Oja P, Borms J, editors. Health enhancing physical activity Oxford: Meyer & Meyer Sport; 2004. p. 209–37.
15. Stamatakis E, Hamer M, Lawlor DA. Physical activity, mortality, and cardiovascular disease: is domestic physical activity beneficial? The Scottish Health Survey–1995, 1998, and 2003. Am J Epidemiol. 2009;169(10):1191–200.
16. Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. Int J Obes (Lond). 2005; 29(8):894–902.
17. Schnohr P, Lange P, Scharling H, Jensen JS. Long-term physical activity in leisure time and mortality from coronary heart disease, stroke, respiratory diseases, and cancer. The Copenhagen City Heart Study. Eur J Cardiovasc Prev Rehabil. 2006;13(2):173–9.
18. World Health Organization. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41(2):105–14.
19. Lowel H, Doring A, Schneider A, Heier M, Thorand B, Meisinger C. The MONICA Augsburg surveys—basis for prospective cohort studies. Gesundheitswesen. 2005;67(Suppl 1):S13–8.
20. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993;25(1):71–80.
21. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995;273(5): 402–7.
22. Hense HW, Filipiak B, Döring A, Stieber J, Liese A, Keil U. Ten year trends of cardiovascular risk factors in the MONICA Augsburg region in southern Germany: Results from the 1984/ 1985, 1989/1990, and 1994/1995 surveys. CVD Prevention. 1998;1(4):318–27.
23. Keil U, Stieber J, Doring A, Chambless L, Hartel U, Filipiak B, et al. The cardiovascular risk factor profile in the study area Augsburg. Results from the first MONICA survey 1984/85. Acta Med Scand Suppl. 1988;728:119–28.
24. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? Med Sci Sports Exerc. 2001;33(6 Suppl):S459–71. discussion S93–4.
25. Orsini N, Mantzoros CS, Wolk A. Association of physical activity with cancer incidence, mortality, and survival: a population-based study of men. Br J Cancer. 2008;98(11):1864–9.
26. Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. Med Sci Sports Exerc. 2003;35(11): 1823–7.
27. Thune I, Furberg AS. Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. Med Sci Sports Exerc. 2001;33(6 Suppl):S530–50. discussion S609–10.
28. Laukkanen JA, Rauramaa R, Makikallio TH, Toriola AT, Kurl S. Intensity of leisure-time physical activity and Cancer mortality in men. Br J Sports Med. 2009. doi:10.1136/bjsm.2008.056713.
29. Vatten LJ, Nilsen TI, Holmen J. Combined effect of blood pressure and physical activity on cardiovascular mortality. J Hypertens. 2006;24(10):1939–46.
30. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2002;136(7):493–503.
31. Koster A, Harris TB, Moore SC, Schatzkin A, Hollenbeck AR, van Eijk JT, et al. Joint associations of adiposity and physical activity with mortality: the National Institutes of Health-AARP Diet and Health Study. Am J Epidemiol. 2009;169(11):1344–51.
32. Oguma Y, Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and all cause mortality in women: a review of the evidence. Br J Sports Med. 2002;36(3):162–72.
33. Iqbal R, Rafique G, Badruddin S, Qureshi R, Gray-Donald K. Validating MOSPA questionnaire for measuring physical activity in Pakistani women. Nutr J. 2006;5:18.
34. Roeykens J, Rogers R, Meeusen R, Magnus L, Borms J, de Meirleir K. Validity and reliability in a Flemish population of the WHO-MONICA Optional Study of Physical Activity Questionnaire. Med Sci Sports Exerc. 1998;30(7):1071–5.

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Erklärung

Hiermit erkläre ich, Christine Autenrieth, dass ich die vorliegende Dissertation selbstständig angefertigt habe. Ich habe mich außer der angegebenen keiner weiterer Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen. Ich habe bisher noch keinen Promotionsversuch unternommen, und die vorliegende Dissertation wurde nicht in gleicher oder ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht.

München, den 29. August 2012

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