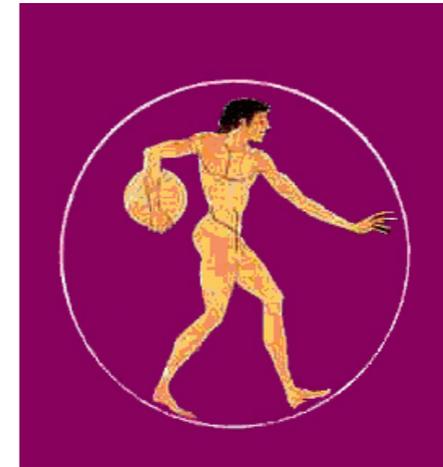


Thesis for doctoral degree (Ph.D.)
2008

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Physical activity and health benefits

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Nicola Orsini

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**Karolinska
Institutet**



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Division of Nutritional Epidemiology
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**Karolinska
Institutet**

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To my family

ABSTRACT

Physical activity (PA), due to its role in health promotion and disease prevention, is of particular interest to be investigated. The aims of this thesis were: to assess the associations between PA and different health outcomes (lower urinary tract symptoms, cancer incidence, and mortality) in the Cohort of Swedish Men (COSM); to perform a dose-response meta-analysis of published associations between walking and incidence of coronary heart disease (CHD); and to provide user-friendly software packages for dose-response meta-analysis and for sensitivity analysis of biases in observational studies. The COSM is a population-based prospective cohort of 45,906 men between 45 to 79 years of age in central Sweden who were cancer-free and completed a questionnaire about current and historical PA, diet, and other life-style factors at enrollment in 1997.

At baseline 6905 men reported moderate to severe lower urinary tract symptoms (LUTS). A significant inverse relationship was seen between total PA and moderate and severe LUTS (highest vs lowest quartile odds ratio=0.72; 95% confidence interval (CI)=0.66-0.79). Men who were physically active at work as well as during leisure-time showed 50% reduction in risk of moderate to severe LUTS (95% CI=0.40-0.60) compared to those who were sedentary. Conversely, men with long-term sedentary lifestyles (5 hours/day watching TV both at age 30 years and current) reported a 2-fold increase (95% CI=1.41-2.59) risk to these symptoms when compared to men more active at both time periods.

After 7 years of study enrollment 3714 men of the COSM were diagnosed with cancer and 1153 of them died due to the disease. We observed a strong inverse linear association between total daily PA and death from any form of cancer. For each increment of 4 metabolic equivalent (MET)-hours/day of total PA (approximately 1 hour daily of moderate effort) cancer incidence tended to be decreased by 2% and cancer mortality decreased significantly by 12% (95% CI = 6-18%).

During 9.7 years of follow-up, we identified a total of 4086 deaths from all causes. Compared to men who were lean and active (BMI < 25 kg/m²; top tertile total PA) the adjusted rate ratios of death from all causes were 1.44 (95% CI=1.11-1.86) for obese-active men (BMI ≥ 30 kg/m²), 1.54 (95% CI=1.34-1.77) for lean but inactive men (bottom tertile total PA), and 1.81 (95% CI=1.48-2.23) for obese-inactive men. After excluding the first 3 years of follow-up, current and former smokers, those who had lost weight from age 20 years to baseline, and heavy manual workers, the adjusted rate ratios of death from all causes were 1.65 (95% CI=1.20-2.27) for overweight-to-obese and active men, 2.15 (95% CI=1.59-2.91) for lean-inactive men, and 2.04 (95% CI=1.52-2.74) for overweight-to-obese and inactive men compared to lean-active men.

During 10 years of follow-up a total of 2735 men were diagnosed with prostate cancer, of which 190 were fatal. We observed an inverse linear association between lifetime (average of age 30, 50 and baseline) walking/bicycling duration and incidence of total prostate cancer risk. The multivariable-adjusted rate ratio decreased by 8% (95% CI=2-13%) for every 30 min/day increment of lifetime walking/bicycling in the range of 30 to 120 min/day. The fatal prostate cancer rate among those men who hardly ever walked or biked was two-fold that of men in the highest average lifetime walking/bicycling of 120 min/day, although this increased rate was not significant.

In the dose-response meta-analysis of eight epidemiological studies we found that every increment of 8 MET-hours/week of walking (moderate-intensity about 30 min/day on 5 days of the week) was associated with 19% decrease (95% CI=14-23%) of CHD risk.

In conclusion, we observed that increased PA levels may lower the risk of LUTS, all-cause and cancer mortality, prostate cancer, and CHD. Furthermore, the two statistical components developed for Stata® software can greatly facilitate dose-response meta-analyses (**glst**) and support sensitivity analysis (**episens**) of epidemiological findings.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to their Roman numerals:

- I. **Orsini N**, RashidKhani B, Andersson S-O, Karlberg L, Johansson J-E, and Wolk A. Long-term physical activity and lower urinary tract symptoms in men. *Journal of Urology*, 2006, 176(6):2546-50; discussion 2550.
- II. **Orsini N**, Mantzoros, CM., Wolk A. Association of physical activity with cancer incidence, mortality, and survival: a population-based study of men. *British Journal of Cancer*, 2008, 98 (11):1864-9.
- III. **Orsini N**, Bellocco R, Bottai M, Michaelsson K, Pagano M, Wolk A. Combined effects of obesity and physical activity in predicting mortality among men. *Journal of Internal Medicine*, 2008, 264 (5): 442 - 451.
- IV. **Orsini N**, Bellocco R, Bottai M, Andersson S-O, Karlberg L, Johansson J-K, Wolk A. A prospective study of lifetime average walking/bicycling duration and incidence and fatal prostate cancer. 2008, *submitted*.
- V. Zheng H, **Orsini N**, Wolk A, Amin J, Nguyen Van TT , Leeder S, Ehrlich F, Quantifying the dose-response between walking and reduced coronary heart disease risk: Meta-Analysis. 2008, *submitted*.

Methodological papers

- VI. **Orsini N**, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata Journal*, 2006, 6 (1): 40-57.
- VII. **Orsini N**, Bellocco R, Bottai M, Wolk A, Greenland S. A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies. *Stata Journal*, 2008, 8 (1): 29-48.

LIST OF RELATED PUBLICATIONS

Orsini N, Bellocco R, Bottai M, Hagströmer M, Sjöström M, Pagano M, Wolk A. Validity of self-reported total physical activity among older women. *European Journal of Epidemiology*, 2008, 23(10):661-7.

Orsini N, Bellocco R, Bottai M, Hagströmer M, Sjöström M, Pagano M, Wolk A. Profile of physical activity behaviors among Swedish women aged 56-75 years. *Scandinavian Journal of Medicine & Science in Sports*, 2008, 18(1):95-101.

Orsini N, Bellocco R, Bottai M, Pagano M, Wolk A. Correlates of total physical activity among middle-aged and elderly women. *International Journal of Behavioral Nutrition and Physical Activity*, 2007, 4:16.

Orsini N, Bellocco R, Bottai M, Pagano M, Wolk A. Reproducibility of the past year and historical self-administered total physical activity questionnaire among older women. *European Journal of Epidemiology*, 2007, 22 (6):363-8.

Orsini N, Bellocco R, Bottai M, Pagano M, Wolk A. Age and temporal trends of total physical activity among Swedish women. *Medicine & Science in Sports & Exercise*, 2006, 38: 240-5.

Selected publications using the dose-response meta-analysis command (Paper VI)

Larsson SC, **Orsini N**, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. *International Journal of Cancer*, 2007,1;120(9):1993-8.

Larsson SC, **Orsini N**, Wolk A. Processed meat consumption and stomach cancer risk: a meta-analysis. *Journal National Cancer Institute*, 2006, 2; 98(15):1078-87.

Larsson SC, **Orsini N**, Wolk A. Milk, milk products, and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *International Journal of Cancer*, 15; 118(2):431-41.

Suzuki R., **Orsini N**, Mignone L., Saji S., Wolk A. Alcohol Intake and Risk of Breast Cancer Defined by Estrogen and Progesterone Receptor Status - A meta-analysis of epidemiological studies. *International Journal of Cancer*, 2008, 122(8):1832-41.

Suzuki R., **Orsini N**, Saji S., Wolk A. Body Weight and Incidence of Breast Cancer Defined by Estrogen and Progesterone Receptor Status - A meta-analysis. *International Journal of Cancer*, 2008, in press.

From January 2006 through October 2008 Paper VI (Orsini, *et al.* 2006) has been used and/or cited 27 times. A complete list and updated information is available at:

<http://nicolaorsini.altervista.org/stata/tutorial/g/glst.htm>

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LIST OF ABBREVIATIONS

BMI	Body mass index
BPH	Benign prostatic hyperplasia
CI	Confidence interval
COSM	Cohort of Swedish men
IPSS	International prostate symptom score
LUTS	Lower urinary tract symptoms
MET	Metabolic equivalent
MICE	Multiple imputations by chained equations
OR	Odds ratio
PA	Physical activity
RR	Rate ratio
WHR	Waist-to-hip ratio

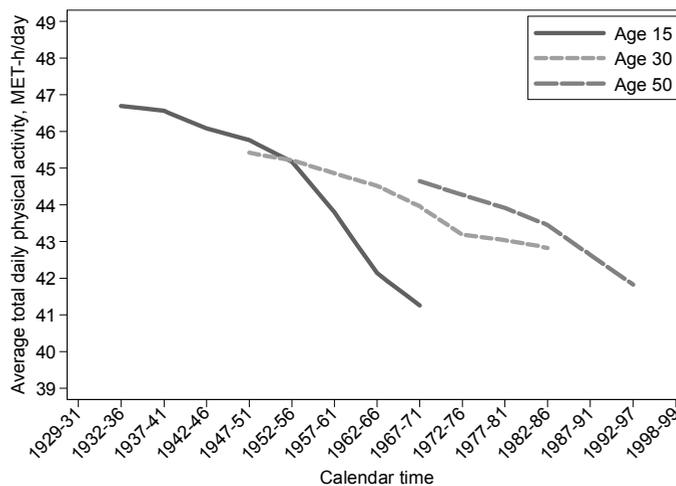
1 INTRODUCTION

Physical activity (PA) is a health-related behavior that has been an important factor in the prevention, management, and rehabilitation of many chronic diseases and conditions such as cardiovascular disease, hypertension, osteoporosis, obesity, type II diabetes, hip fracture and certain forms of cancer (PAGAC 2008, WCRF/AICR 2007). Because of its role in health promotion and disease prevention, PA is a particularly important health behavior to be investigated. Interest in PA as a means of disease prevention is increasing as PA proves to be one of the few risk factors that can be modified through lifestyle/behavior changes. PA includes not just exercise and sports, but all movement that occurs in the course of daily living, including home/household work, self-transportation, and occupational activities.

Although it is widely accepted that PA is important for health, one of the greatest challenge remains the measurement of PA. Questionnaires used for estimating habitual PA in large-scale epidemiological studies differ in focus, time period, and data collecting method (Jacobs, *et al.* 1993). Most questionnaires measure only a fraction of the PA, for example PA at work, sport or leisure-time activities, while in fact the total volume of PA may be of more relevance.

Scarce information is available on temporal trends for total PA in various populations. In the United States one systematic review of PA trends over the past 50 years showed that declines have occurred in work-related activity, transportation, home activity, resulting in overall decrease in total PA levels (Brownson, *et al.* 2005). Findings from our research group based on a large population-based cohort of middle-aged and elderly men show that total PA has been decreasing by calendar time during the last 60 years of the 20th century (Norman, *et al.* 2003) (Figure 1.1).

Figure 1.1 Temporal trends of the average total daily physical activity by calendar time in different age groups in middle-aged and elderly Swedish men.



Despite a large public health interest in PA many research questions remained to be answered in the field of PA epidemiology. The purpose of this thesis was to evaluate the role of PA in relation to different health outcomes.

2 BACKGROUND

2.1 HEALTH BENEFITS RELATED TO PHYSICAL ACTIVITY

Since ancient times, more than 2000 years ago, Greek physicians recognized and emphasized the importance of physical well-being and healthy lifestyle (MacAuley 1994). However, the modern epidemiology of PA began with Professor Jeremy N. Morris and his associates in the 1950s and focused on occupational PA and the epidemic of cardiovascular disease. Professor Ralph Paffenberger and other investigators in the United States and Europe expanded Morris' work during the 1960s and 1970s (Erllichman, *et al.* 2002, Paffenbarger, *et al.* 2001).

Based on the mounting evidence and international consensus of beneficial effects of PA a key document published in 1992 by the American Heart Association recognized physical inactivity as an independent risk factor for coronary heart disease morbidity and mortality (Fletcher, *et al.* 1992).

The first public health recommendation on PA and health was prepared jointly by the Centers for Disease Control and the American College of Sports Medicine and released in 1995: every adult should accumulate moderate-to-vigorous activity at least 30 minutes on most days, preferably all days of the week (Pate, *et al.* 1995). This PA recommendation has been adopted in many countries, as well as in Sweden (National Institute of Public Health 2005). Compared to early exercise prescriptions of vigorous activity the PA recommendation was innovative in two aspects: moderately intensive activity (using brisk walking as a benchmark) and accumulation of activity throughout the day in short bouts lasting 8 to 10 minutes.

In the 1996 historical benchmark *Physical Activity and Health: A Report from the Surgeon General* nearly 100 experts outlined the consensus in the scientific community about the beneficial effects of PA on overall mortality, cardiovascular disease, type 2 diabetes, osteoporosis, obesity, mental health, health-related quality of life, risk of musculoskeletal injury, and risk of sudden death (USDHHS 1996).

In 2007 the World Cancer Research Fund and American Institute of Cancer Research systematically reviewed and assessed the body of evidence on diet, PA and cancer and published a Second Expert Report (WCRF/AICR 2007). The personal PA recommendation to reduce risk of developing cancer was to be moderately physically active, equivalent to brisk walking for at least 30 minutes every day. As fitness improves, one should aim to 60 minutes or more of moderate, or 30 minutes or more of vigorous PA every day.

A comprehensive review and analysis of the latest knowledge about PA and health was recently released by the U.S. Department of Health and Human Services (PAGAC 2008). The sum of the evidence provided in the *Physical Activity Guidelines Advisory Committee Report, 2008* for a wide range of health and fitness outcomes (cardiorespiratory health, metabolic health, mental health, musculoskeletal health, functional health, cancer, all-cause mortality) strongly supports the value of being physically active versus being sedentary throughout the lifespan. Unsurprisingly, increasing participation in regular PA is a world health priority for many developed and developing countries. However, according to the World Health Organization, at least 60% of the world's population fails to complete the recommended amount of PA required to induce health benefits.

The remaining part of the paragraph provides some descriptive epidemiology of the specific health outcomes investigated in this thesis: lower urinary tract symptoms, cancer, cardiovascular disease, and mortality.

Lower urinary tract symptoms

The term lower urinary tract symptoms (LUTS) is now universally recognized as the preferred terminology to describe a constellation of symptoms that may be caused by multiple pathologic conditions such as benign prostatic hyperplasia (BPH). LUTS and BPH are highly prevalent conditions among older men and the prevalence increases with age.

Our research group previously assessed the prevalence of LUTS in a large population-based study of Swedish men 45 to 79 years of age (Andersson, *et al.* 2004). Overall, about 23% of the men were moderately to severely symptomatic; the prevalence of at least one symptom was 83%. Furthermore, LUTS were strongly age-dependent, with 1.8% of severe symptoms among men aged 45–49 years and increasing to 9.7% among those 75–79 years old (Andersson, *et al.* 2004).

The origin of BPH remains to be elucidated. Traditional causal models have focused on hormones and genetic predisposition. However, accumulating evidence indicated that also modifiable risk factors (PA, diet, and alcohol consumption) may substantially contribute to the history of BPH and LUTS (Parsons 2007, Parsons and Kashefi 2008).

Cancer

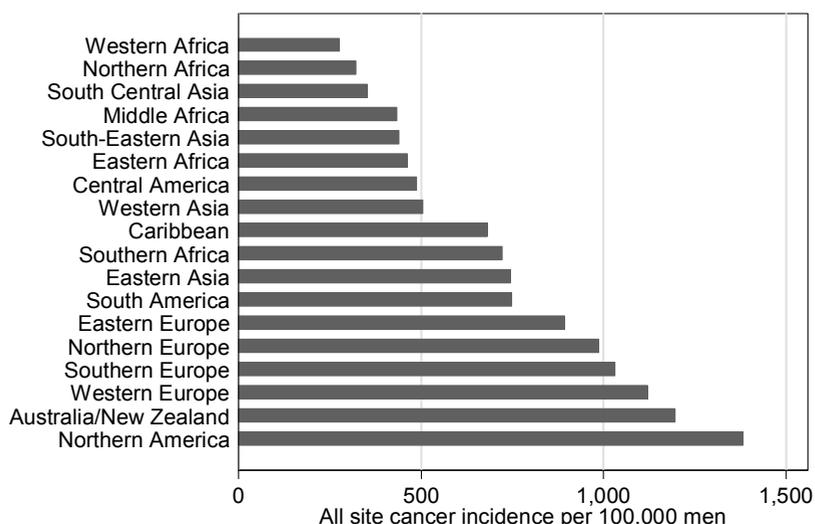
Cancer is a disease of genes that can affect any part of the body over the long human lifespan. The rapid creation of abnormal cells that grow beyond their usual boundaries can spread to other organs. This process is referred to as metastasis which is the major cause of death from cancer. Although genetic inheritance influences the risk of cancer, both epidemiological and experimental evidence have shown that only a small proportion of cancers are inherited (WCRF/AICR 2007).

Patterns of cancer and trends, incidence, and projections vary greatly in different parts of the world (Figure 1.2). Global disparities in cancer incidence are evident and likely due to complex interactions of risk factors that are non-modifiable (i.e., genetic susceptibility and aging) and modifiable (i.e., tobacco, infectious agents, diet, and PA) (Kamangar, *et al.* 2006). Life-style and environmental factors are important in determining the likelihood of some mutations, as well as in changing the functions of genes even without any mutation. Systematic work has already led authoritative independent organizations to be confident that most cancers are largely preventable (WCRF/AICR 2007). Behaviors such as avoiding exposure to tobacco products, maintaining a healthy weight, staying physically active throughout life, and consuming a healthy diet can substantially reduce one's lifetime risk of developing cancer (Kushi, *et al.* 2006).

In 2006, a total of 50,776 cases of cancers were reported in Sweden, of these 53% were men. Figure 1.3 shows the trend in cancer incidence from all sites among men aged 45 years or more (Data source: <http://www.socialstyrelsen.se/en/Statistics/>). During the last two decades the average annual increase has been 1.7% for men. The increase is partly explained by the aging population but also by the introduction of screening activities and improvements in diagnostic practices. Prostate cancer is the most common cancer in men, representing 34.6% of the male cases in 2006. On average, the incidence has increased by 2.9% annually as seen over the last 20 years (Figure 1.4). Skin cancer (excluding malignant melanoma) is the second common

cancer and has the highest annual increase (3.2%) during the last 20 years. Colon cancer is the third most frequent type of cancer constituting 6.8% of the cases. Currently, in Sweden, approximately 162,000 men are battling any given form of cancer.

Figure 1.2 Incidence rates for cancer in all sites among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the world population.



Data source: International Agency for Research on Cancer, GLOBOCAN

Cardiovascular disease

The heart, like any other muscle, requires blood to supply oxygen and nutrients for it to function. It beats about 100,000 times a day, pumping blood through the circulatory system. The cycle of pumping blood throughout the body carries fresh oxygen to the lungs and nutrients to the body's tissues. Blood also takes waste, such as carbon dioxide, away from the tissues, without this process, we could not live. The main forms of heart or cardiovascular disease (CVD) are coronary heart disease (CHD) and stroke, which are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. Myocardial infarction is the most common diagnosis within CHD.

Compelling evidence from epidemiologic studies supports that PA is inversely and strongly related to cardiovascular morbidity and mortality (e.g., heart attack and stroke) (PAGAC 2008). The inverse association habitual PA and CVD exists across a wide range of types, amount, and intensity of activity. More importantly, most of the modifiable risk factors for CVD (hypertension, dyslipidemia, type 2 diabetes, and obesity) are modifiable by changes in PA levels (PAGAC 2008).

In 2005, a total of 26,720 men aged 45 or more were diagnosed acute myocardial infarction or any other ischemic heart disease in Sweden. Figure 1.5 shows a decreasing trend of the incidence of acute myocardial infarction or any other ischemic heart disease over the last 20 years in Sweden.

Figure 1.3 Temporal trend for cancer incidence from all sites among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the Swedish population.

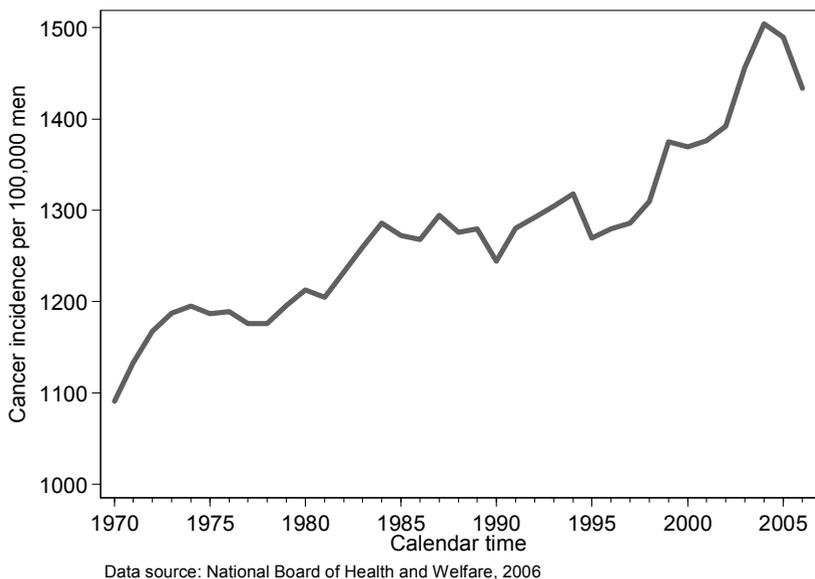


Figure 1.4 Temporal trend for prostate cancer incidence among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the Swedish population.

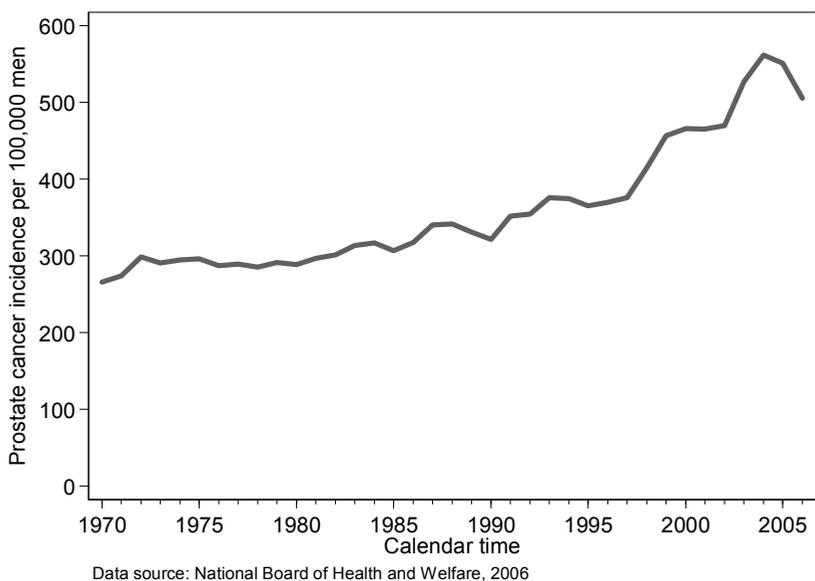
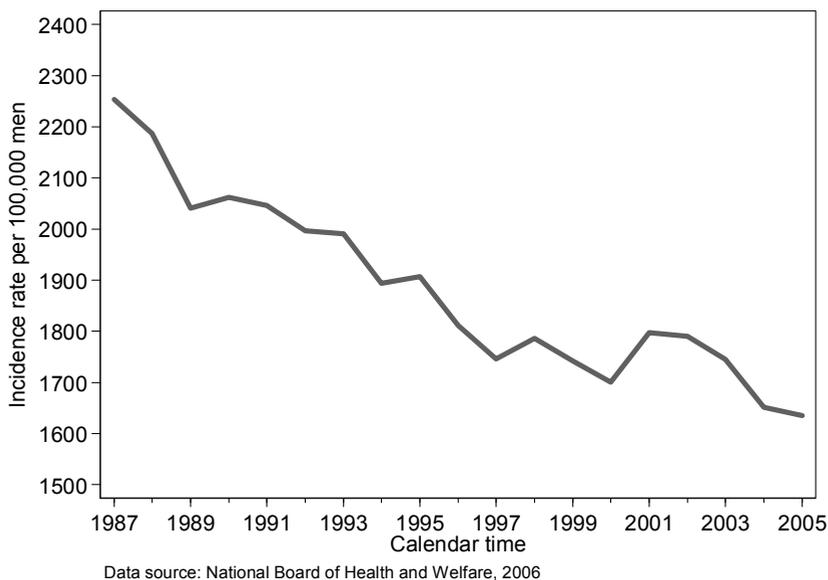


Figure 1.5 Temporal trend for incidence of acute myocardial infarction or any other ischemic heart disease among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the Swedish population.



Mortality

It is widely accepted that people's behavior influences their health and risk of premature mortality, therefore understanding the role of PA in reducing mortality risk has a great public health importance in any developed or developing nations.

Diseases of the circulatory system (CVD) and cancer are the leading causes of death worldwide. The World Health Organization estimated 17.5 million deaths from CVDs, representing about one third of all global deaths. Of these deaths, an estimated 7.6 million were due to CHD. Furthermore, cancer accounted for 7.9 million deaths; around 13% of all deaths.

In Sweden mortality rates from all causes and circulatory system are falling since 1997 (Figure 1.6). Almost half of all deaths had a circulatory disease as the underlying cause of death. The total cancer mortality trend also slightly decreased over time. Cancers from digestive, genital, and respiratory organs accounted for the majority (approximately 70%) of all cancer deaths (Figure 1.7).

Reviews of epidemiological data supported a steep inverse dose-response gradient between PA and premature death from all causes (Blair and Wei 2000, PAGAC 2008). The 73 studies included in the recent review (PAGAC 2008) have assessed one or more domains of PA (i.e., leisure-time, occupational, household, and active commuting), with most assessing primarily leisure-time PA. Furthermore, some evidence indicated that it may be the overall volume of energy expended – regardless of the specific type of activity– that is important to lower the mortality risk during follow-up time.

Figure 1.6 Temporal trend for all cause, circulatory system, and cancer mortality rate among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the Swedish population.

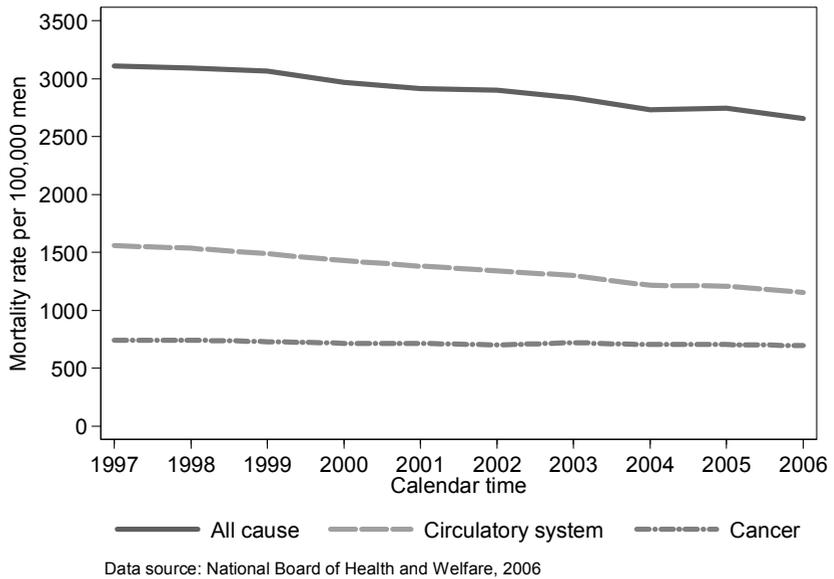
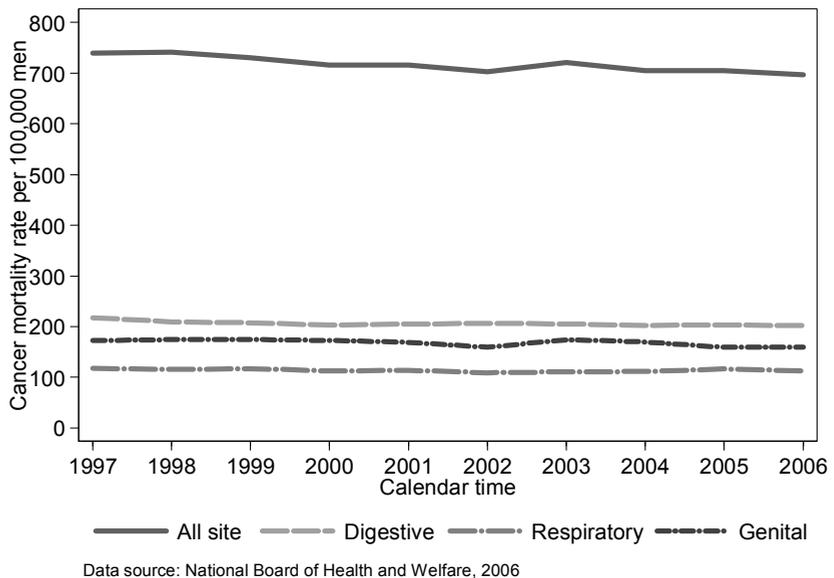


Figure 1.7 Temporal trend of cancer mortality rate from all-cause, digestive, genital, and respiratory organs among men aged 45 years or more, expressed per 100,000 persons and age-standardized according to the Swedish population.



2.2 DEFINITION AND ASSESSMENT OF PHYSICAL ACTIVITY

PA is any body movement that is produced by the skeletal muscles and that results in energy being expended by the body (Caspersen, *et al.* 1985). PA does not necessarily mean running a strenuous marathon or playing competitive sports. Rather, for many people, it is about walking the children to school, or taking a brisk stroll in the park. It means taking the stairs, instead of the elevator, or getting off the bus two stops early.

Although many people think of exercise as the quintessential form of PA, PA encompasses more than just exercise. Exercise is activity that is planned and structured, with the main objective of improving or maintaining physical fitness. Examples of exercise include participating in sports such as swimming, taking aerobics classes, jogging, or brisk walking for health. PA, on the other hand, also includes all the movement that occurs in the course of doing housework or yard work, commuting, occupational activities, moving from one location to another and other activities of daily living, in addition to exercise, sports, or other recreational activity.

Components of total energy expenditure include basal metabolic rate, which encompasses 50%-70% of total energy expenditure; the thermic effect of food, which accounts for another 7%-10%; and PA (Ravussin and Bogardus 1992). Physical fitness is “a set of attributes either health or performance related”, such as cardiorespiratory, muscular, metabolic, and morphologic attributes that people have or achieve that relate to the ability to perform PA (Caspersen, *et al.* 1985). Moreover, it is important to differentiate between PA and energy expenditure (Lamonte and Ainsworth 2001). PA is a behavior that results in energy expenditure while energy expenditure reflects the energy cost or intensity associated with a given PA.

Individuals undertake PA in several domains of their daily lives, and all individuals are experiencing some levels of PA. A complete assessment of PA should include all its components: frequency, duration, and intensity, in all domains of daily living, throughout the life course. When considering the assessment of PA, it is important to acknowledge the multidimensional nature of the term. Frequency and duration describe the number of times that the activity is undertaken in a given period and the total time spent in PA during the same period (e.g. “for 15 minutes, two times per day”). Intensity describes the amount of work that the activity requires, and is often classified as light, moderate or vigorous. In general terms, moderate PA causes some increase in breathing or heart rate. Examples include housework, childcare activities, occupational activity, or walking for transportation. Vigorous activity causes a large increase in breathing or heart rate and conversation becomes difficult or ‘broken’. Examples of vigorous activity include jogging, in high-impact aerobic dancing, swimming continuous laps, bicycling uphill, or standing or walking with more than 10 kilograms.

Physical activities are often classified into domains that reflect the purpose of the activity. A common classification is: occupational (work), domestic (housework, yard work, and physically-active child care), transportation (walking or bicycling for the purposes of going somewhere), and leisure-time (discretionary or recreational time for hobbies, sports, and exercise).

Objective measurement of physical activity

There is currently no “gold standard” for measuring PA in a large population sample. The double-labeled water method is considered the most accurate method, it measures the disappearance rate of labeled water isotopes from urine samples to estimate carbon

dioxide production (Schoeller and van Santen 1982). A limitation of this technique – besides the fact that it is very costly and unsuitable for large-scale studies – is that it does not discriminate activity patterns or permit evaluation of exercise intensity. Another method, heart rate monitoring is based on the linear relationship between heart rate and oxygen consumption and provides an indication of intensity, duration and frequency of an activity, but may be influenced by factors other than PA (Melanson and Freedson 1996). Moreover, the linear relationship may not be accurate during low and very high intensity activity (Lamonte and Ainsworth 2001). Accelerometers are small computer motion sensors, which measure intensity, duration and frequency of activity. The use of accelerometers to measure activity is based on the assumption that accelerations of the limbs and torso closely reflect energy cost but the specific type of PA is unknown (Lamonte and Ainsworth 2001).

The current best-practice method for assessing the criterion validity of self-recall questions on the intensity, duration and frequency of PA undertaken in specific domains, is probably a combination of accelerometers and log books (Ainsworth, et al. 2000). The use of accelerometers is recommended in conjunction with log books to enable information to be collected on the type of PA irrespective of its usage for non-leisure or leisure-time PA recordings.

Self-reported physical activity

Although somewhat limited in its objectivity, self-reported PA is commonly used in large-scale epidemiological studies, since it is relatively easy to administer and comparatively inexpensive (Melanson and Freedson 1996).

PA questionnaires used vary in their complexity, from self-administered, single-item questions to interviewer-administered surveys of lifetime PA (Haskell, *et al.* 1992, Pereira, *et al.* 1997). Activity questionnaires can either ask about usual average activity or ask about activity performed within a specific period in time, e.g. ranging from hourly to over a lifetime. Questionnaires focusing on a longer time frame, such as one year, may be more likely to reflect usual activity patterns. Most of the questionnaires measure only a fraction of the PA, for example, activity at work, sporting frequency or leisure-time activities (Albanes, *et al.* 1990, Melanson and Freedson 1996, Pereira, *et al.* 1997) and the two principal categories of PA used are occupational PA and leisure-time activity. Occupational activity usually refers to 8-hours per day, whereas the duration of leisure-time PA is quite variable and based on personal interests and needs including formal exercise programs, walking, hiking, gardening, sport, dance etc (Howley 2001). Exercise is a subcategory of leisure-time PA performed to improve or maintain physical fitness as described above (Howley 2001). Household activities also contribute to the daily PA and are important to include in the questionnaire.

Time considerations often require the use of brief surveys that measure the most common physical activities of a population. Estimating only a part of PA (i.e. occupation, leisure-time) may give a vague understanding of the habitual levels of total daily PA. Moreover, it is not always clear whether a specific type of activity or the overall level of PA is related to health benefits (Haskell, *et al.* 1992).

3 AIMS

The general objective was to examine the role of physical activity levels in relation to several health outcomes among middle-aged and elderly men.

The specific aims were:

- To assess the association between current and distant physical activity and the risk of lower urinary tract symptoms (Paper I).
- To evaluate the association between physical activity and cancer incidence, mortality and survival after cancer diagnosis (Paper II).
- To investigate the combined effects of obesity and physical activity in predicting all cause and cause-specific mortality (Paper III).
- To assess the association between average lifetime walking/bicycling duration and prostate cancer risk (Paper IV).
- To quantitatively summarize the dose-response association between walking and coronary heart disease risk (Paper V).

The aim of the methodological papers was to provide the tools for:

- trend estimation based on summarized dose-response data (Paper VI).
- sensitivity analysis of epidemiological studies (Paper VII).

4 METHODS

4.1 THE COHORT OF SWEDISH MEN

The general aim of the Cohort of Swedish Men (COSM) was to assess relationships between a number of modifiable factors and the occurrence of several major diseases.

The population-based COSM was established in 1997-1998, when all men ($n=100,303$) aged 45 to 79 years residing in Västmanland and Örebro counties (central Sweden) received an invitation to participate in the study. A questionnaire accompanying the invitation included questions about PA, current weight, height, education, cigarette smoking, alcoholic beverages, diabetes, family history of cancer, and other lifestyle factors. A total of 48,645 men returned the questionnaire.

In all papers we excluded participants who returned a blank questionnaire ($n=92$), who died before January 1, 1998 ($n=55$), and those men with previous diagnosis of cancer ($n=2592$), leaving 45,906 men for the analysis (Figure 4.1). According to the health outcome we did further exclusions in each study. For paper I we excluded those who did not provide complete information on PA and urinary tract symptoms ($n=15,529$) leaving 30,377 men for the analysis. For paper II we excluded heavy manual workers ($n=5198$) because overall mortality from cancer has been found to be significantly higher among men with manual occupations (Rosengren and Wilhelmsen 2004) leaving a cohort of 40,708 men. For paper III we excluded men with cardiovascular disease ($n = 5069$) and diabetes ($n = 3204$) at baseline leaving a cohort of 37,633 men. For paper IV we excluded those men who moved out of the study area ($n=19$) leaving a cohort of 45,887 men.

Representativeness of the cohort

Our large population-based cohort represents well the whole Swedish male population 45 to 79 years old in terms of distribution of age, body mass index, and educational level (Table 4.1).

Table 4.1 Comparison of the baseline Cohort of Swedish Men (COSM) with the Swedish population in 1997 for men between 45 to 79 years of age, regarding age composition, body mass index, and educational level.

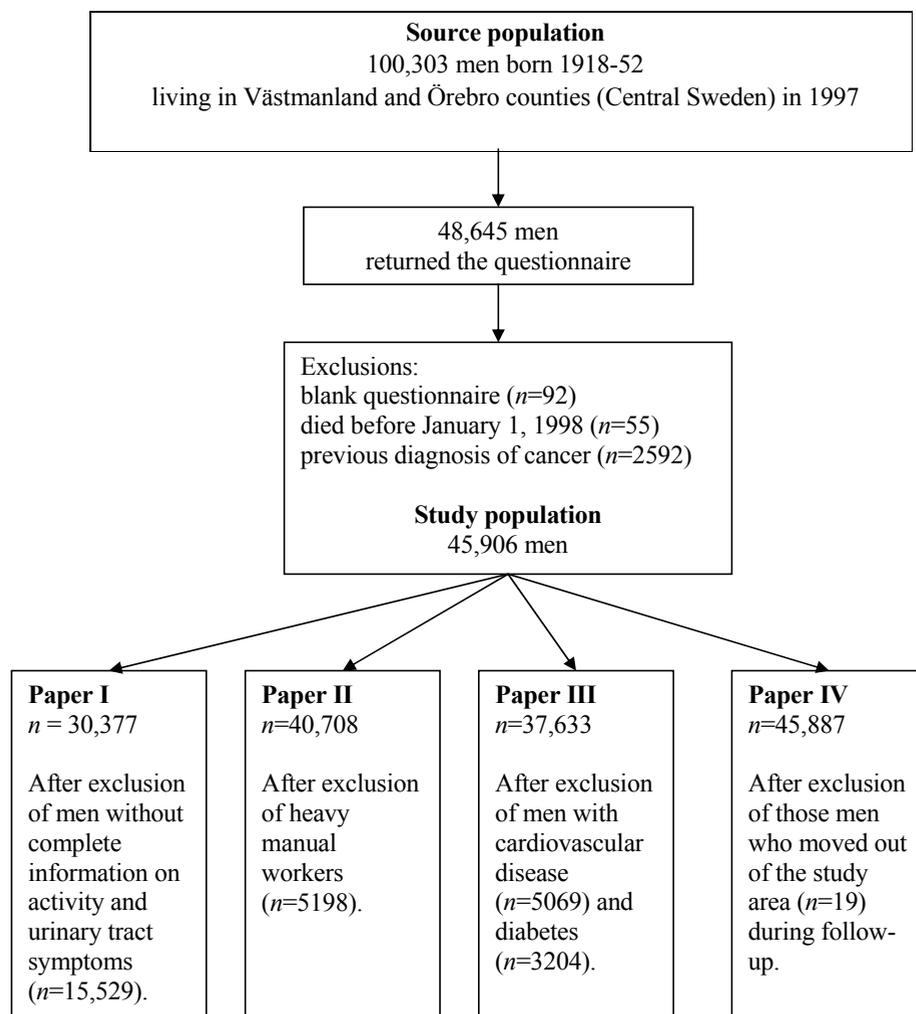
Characteristics	COSM $n=45,906$ %	Swedish population ^a $n=1,594,952$ %
Age group, years^a		
45-64	64	68
65-79	36	32
Body mass index, kg/m²^b		
< 25	44	45
≥ 25	56	55
Education, years^a		
≥ 12	16	19

^a Available from Official Statistics of Sweden (Data source: <http://www.scb.se>).

^b Available only prevalence of overweight from (Lissner, *et al.* 2000).

Figure 4.2 shows a comparison of the COSM with the entire Swedish population in 1997 for men between 45 to 79 years of age.

Figure 4.1 Source population, exclusions, and study population for Papers I-IV.



4.1.1 Assessment of physical activity

Physical activity questionnaire

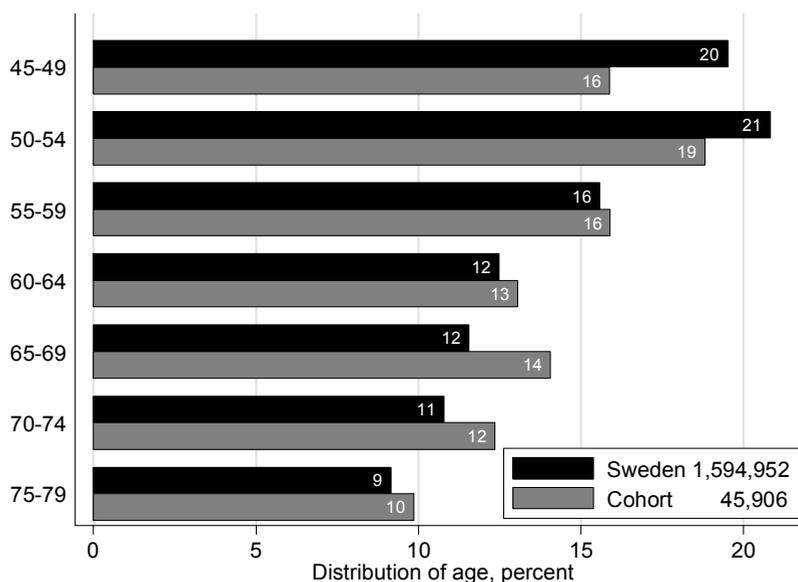
Habitual PA level was assessed using a short self-administered questionnaire. Different types of activities were recalled at current age (1997) and retrospectively at ages 15, 30 and 50 years (Figure 4.3).

Information on PA was collected using five questions (work/occupation, walking/bicycling, home/household work, active, inactive leisure-time watching TV/reading, and leisure-time exercise) about duration and intensity of usual PA.

In the PA questionnaire there were six predefined activity levels for occupational activity (from mostly sitting down to heavy manual labor) and five to six predefined

categories for time spent on different activities: walking/bicycling (from hardly ever to more than one 1.5 hours/day), home/household work (from less than one hour/day to more than eight hours/day), inactive leisure-time watching TV/reading (from less than one hour/day to more than 6 hours/day), and active leisure time exercising (from less than one hour/week to more than five hours/week). There was also an open question about the number of sleeping hours/day.

Figure 4.2 Distribution of age comparing the Cohort of Swedish Men with the entire Swedish population in 1997 for men between 45 to 79 years of age.



Calculations of physical activity levels

PA levels for specific activities were estimated by multiplying reported duration (hours per day) by the absolute intensity. The absolute intensity of an activity is determined by the rate of work being performed and does not take into account the physiologic capacity of the individual. The absolute intensity of activities, defined in multiples of the metabolic equivalent (MET, kcal/kg×hour) of sitting quietly for 1 hour, was based on a compendium of physical activities (Ainsworth, *et al.* 2000).

For the questionnaire, we assigned mean MET values based on specific activities within corresponding categories (Figure 4.3). The total daily PA score was calculated by adding up the products of duration and intensity for each type of physical activities. We corrected the self-reported time to 24 hours per day, by adding the missing hours or subtracting over reported hours. This “correction time” was multiplied by the intensity factor of 2.0 MET, corresponding to the mean of self-care/walking at home (2.5 MET) and sitting (eating, transportation etc 1.5 MET). This correction was based on the assumption that underestimation of time might be due to these common activities not asked for in the questionnaire (Norman, *et al.* 2001).

Figure 4.3 Physical activity questionnaire and assigned mean MET values.

Mark your level of physical activity at different ages:

	Assigned mean MET values ^a (not shown in the questionnaire)				
	15 yrs	30 yrs	50 yrs	this yr	
Work/occupation ^b					
Mostly sitting down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.3
Sitting down half the time	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.8
Mostly standing up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2.2
Mostly walking, lifts, carry <u>little</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2.6
Mostly walking, lifts, carry <u>much</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3.0
Heavy manual labour	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3.9
Walking/bicycling	15 yrs	30 yrs	50 yrs	this yr	3.6
Hardly ever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Less than 20 min/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
20-40 minutes/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40-60 minutes/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1-1,5 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
More than 1,5 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Home/household work	15 yrs	30 yrs	50 yrs	this yr	2.5
Less than 1 hour/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1-2 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3-4 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
5-6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
7-8 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
More than 8 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Leisure-time					
Watching TV/reading	15 yrs	30 yrs	50 yrs	this yr	1.2
Less than 1 hour/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1-2 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3-4 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
5-6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
More than 6 hours/day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Exercise					5.0
Less than 1 hour/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1 hour/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2-3 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4-5 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
More than 5 hours/week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
How many hours of each 24-hour day do you usually sleep?					0.9
<input style="width: 50px; height: 20px; border: 1px solid black;" type="text"/>					hours

a Based on the compendium of physical activities (Ainsworth, *et al.* 2000).

b Daily work/occupational activity levels were inquired for both working and retired men and then multiplied by 5.7 hours of work per day (eight hours per day, five days per week).

Figure 4.4 shows the distribution of the total daily PA score. Figure 4.5 shows the percent contribution of each type of reported activity (averaging individual observations) to the baseline total activity score. Figure 4.6 presents the percent contribution of each type of reported activity within each quartile of the total activity score. Of note, the percent contribution of walking/bicycling in the top quartile of total PA (12%) is twice that of the bottom quartile (6%).

To construct a variable reflecting adult lifetime average daily duration (at age 30, 50, and current) of walking/bicycling, we first assigned middle duration times to the walking/bicycling intervals (0, 10, 30, 50, 75, 120 min/day) and then we calculated the average of recent (current) and distant past (age 50 and 30) walking/bicycling duration times among those men with at least two observed values (91% of the cohort).

Validity and reproducibility of the physical activity questionnaire

Our research group evaluated the validity and reproducibility of the short PA questionnaire intended to assess total daily PA. A total of 111 men randomly selected from central Sweden who completely filled in the first questionnaire and recorded their PA for at least seven days (the reference method was two 7-day records) were included in the analysis (Norman, *et al.* 2001).

To assess the validity of the PA questionnaire, a self-administered structured 7-day PA diary was recorded two times during a year and contained two pages for each day of the week, as well as instructions and an example of a completed day of record. Participants recorded the clock time they started and the time they finished the activity and described all their activities (for example sitting, eating, walking, and sleeping) during 24 hours per day. A subjective estimate of the intensity was recorded by participants for activities such as walking, bicycling, sports etc, by using 1 to 4 “X”-signs, the more intensive, the more “X”-signs that were assigned. Study subjects also recorded the number of stairs climbed every day. All activities recorded were assigned specific MET values taking into account the intensity level when appropriate. The estimate of the average total daily PA was computed by summarizing MET-hours for all specific activities. To assess reproducibility of current and historical PA questionnaire, it was mailed to participants twice in 1998 (January and August).

Our short PA questionnaire was shown to estimate total PA satisfactorily; the correlation between questionnaire and activity records (validity) was 0.56, and between two questionnaires (reproducibility) was 0.65 (Norman, *et al.* 2001). Reproducibility correlations for historical total PA scores at ages 15, 30 and 50 in the validation group were 0.80, 0.78 and 0.82, respectively (Norman 2004).

The PA questionnaire was also tested for validity and reproducibility among 116 women between the ages of 56 and 75 years from the population-based Swedish Mammography Cohort and correlations were overall similar compared to men. Validity correlation comparing total daily activity measured by the questionnaire with the accelerometers and the records were 0.38 and 0.64, respectively (Orsini, *et al.* 2008). Reproducibility correlation for total current PA was 0.69. For historical PA, the reliability coefficients for total PA ranged from 0.75 for age 50 to 0.81 for age 30 years (Orsini, *et al.* 2007).

Figure 4.4 Distribution of baseline total physical activity in the Cohort of Swedish Men, expressed in MET-hours/day.

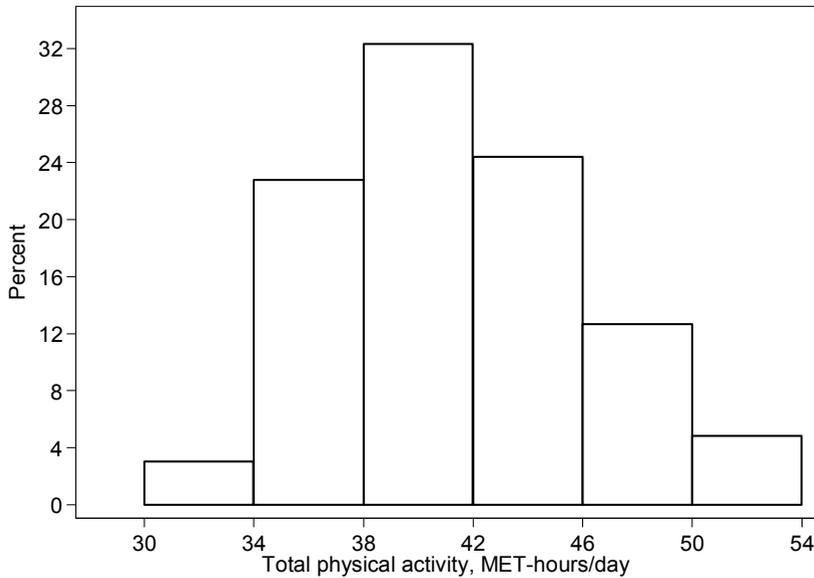
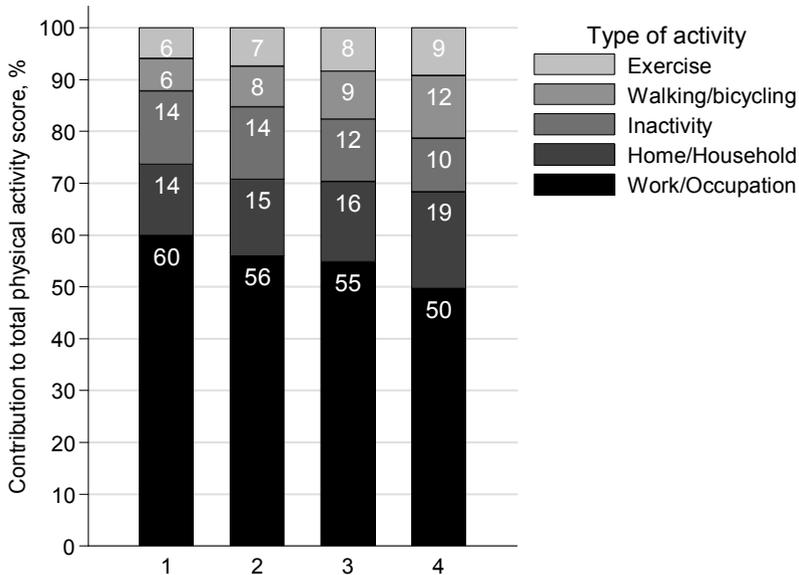


Figure 4.5 Average percent contribution of specific type of activities to the total daily activity score, MET-hours/day.



Figure 4.6 Average percent contribution of specific type of activities within each quartile of the total daily activity score, MET-hours/day.



4.1.2 Case ascertainment

Lower urinary tract symptoms

The questionnaire included questions about presence and severity of urination symptoms. The questions about LUTS were derived from the American Urological Association BPH questionnaire adopted by the World Health Organization as the International Prostate Symptom Score (IPSS) (Barry, *et al.* 1992). The IPSS score has excellent test-retest reliability (correlation was 0.92) and it has been shown to be internally consistent (Cronbach's alpha was 0.86) (Barry, *et al.* 1992).

We used the Swedish version of the IPSS. The questionnaire included questions about presence and severity of six urination symptoms containing fullness (incomplete emptying), frequency (frequent urination), intermittency (urinary stream starts and stops), urgency (sudden, compelling urge to urinate), poor flow (weak stream), and hesitancy (difficulty in starting a urinary stream). This numerical symptom scoring system grades the presence of six symptoms on a discrete scale from 0 to 5 (0=not at all, 1=less than 1 time in 5, 2=less than half the time, 3=about half the time, 4=more than half the time, 5=almost always). We also asked how many times per night the participants had to get up to urinate (0, 1, 2, 3, 4, ≥ 5). A total symptom score was calculated by adding the scores for each of the 6 LUTS and the number of times per night the participant got up to urinate. The range of the total IPSS score was 0 to 35. Men were classified as having mild or no symptoms (0-7 scores) and moderate to severe LUTS (8-35 scores).

Cancer incidence

Date of cancer diagnosis was ascertained by computerized record linkage with the National Swedish Cancer Register and the Regional Cancer Register covering the study area, both of which are estimated to be 100% complete (Mattsson & Wallgren, 1984). Classification of clinical diagnosis of cancer was based on the International Classification of Diseases (ICD-10; all cancers codes C00-C97; prostate cancer code C61).

About prostate cancer, information on Tumor-Node-Metastasis stage, Gleason grade, and value of prostate specific antigen at cancer diagnosis were available from the Swedish Prostate Cancer Quality Registry. Incidence prostate cancer cases were classified according to sub-types as localized (T1-2, NX-0, MX-0 or PSA<20 or Gleason grade \leq 7) and advanced (>T2, NX-1, MX-1 or PSA>100 or Gleason grade >7).

Overall and cause-specific mortality

Date of death was ascertained through linkage to the Swedish Register of Death Causes at the National Board of Health and Welfare which provide nearly 100% complete case ascertainment in Sweden (Rosen 2002). Classification of cause of death was based on the ICD-10 (cardiovascular diseases codes I00-I79; all cancers codes C00-C97; prostate cancer code C61).

4.1.3 Statistical analysis

Paper I

We analyzed the baseline cohort of Swedish men in cross-sectional setting. We estimated odds ratios and corresponding 95% confidence intervals to measure the association between PA and the risk for moderate to severe LUTS. We modeled the odds of moderate to severe LUTS (IPSS \geq 8) using age-adjusted and multivariable-adjusted logistic regression models. We compared the odds of moderate to severe LUTS across total PA quartiles (MET-hours/day) using the lowest quartile as referent group. Final multivariable model included age (continuous), waist-to-hip ratio (quartiles), diabetes (yes, no), alcohol consumption (current drinker, former drinker, never drunk), smoking status (current smoker, former smoker, never smoked), and years of education (<9, 9-12, >12 years) as potential confounders.

The *P*-value for trend was obtained by first creating a new variable containing the median value of total PA within each quartile and then entering it as a continuous variable in the logistic regression models. Statistical interaction was assessed by means of models with and without an interaction term for PA and waist-to-hip ratio and age. The *P*-values for interaction were calculated by likelihood ratio test.

We evaluated the potential effect of missing values on the observed results using multiple imputation analyses (Royston, 2004; van Buuren et al, 1999).

Paper II

The Cox-proportional hazards model was used to estimate incidence and mortality rate ratios and 95% confidence intervals for total PA expressed in MET-hours/day. We treated total PA both as categorized into quartiles and as continuous variables which

allows a more flexible and efficient use of the information available. In our main analysis the endpoints were cancer incidence and cancer mortality in all sites. Each participant accrued follow-up time from January 1, 1998 until the date of cancer diagnosis (for incidence) or cancer death (for mortality), death from any cause, or study end in December 31, 2004, whichever came first. In a secondary analysis, the endpoint was survival after diagnosis of cancer; each men diagnosed with cancer between January 1, 1998 and December 31, 2004 accumulated follow-up time from the date of cancer diagnosis until the date of cancer death, death from any cause, or the end of follow-up (December 31, 2004), whichever occurred first.

Final multivariable model included age (continuous), body mass index (BMI, weight in kilograms divided by the height in meters squared, Kg/m^2 , as continuous) and other potential confounders, including smoking status and pack-years of smoking (never, former < 20 pack-years, former 20-39 pack-years, former \geq 40 pack-years, current < 20 pack-years, current 20-39 pack-years, current \geq 40 pack-years), alcohol consumption (current drinker, former drinker, never drunk), educational level (less than high school, high school graduate, and more than high school), history of diabetes (yes, no), and parental history of cancer (yes, no, not known).

We checked whether the proportional hazard assumption was reasonable in the multivariate models. Scaled Schoenfeld's residuals were calculated, regressed against survival time, and tested for a nonzero slope. There was no evidence of departure from the assumption. We used restricted cubic splines to flexibly model the association between total PA and cancer incidence and mortality rates from all sites. Three knot positions were specified for total PA in MET-hours/day corresponding to the 25th, 50th and 75th percentiles of the observations. We assessed whether age, BMI, and smoking status were effect modifiers of the association between PA and cancer mortality with the Wald test. We evaluated the potential effect of missing values on the observed results using multiple imputation analyses (Royston, 2004; van Buuren et al, 1999).

In our secondary analysis among 2551 men diagnosed with cancer with complete information about PA and potential confounders, 598 men died due to cancer. Cumulative survivor functions for low (bottom quartile), medium (second and third quartile), and high (top quartile) total PA level were estimated using a multivariable Cox regression model and plotted versus time since cancer diagnosis.

Paper III

The Cox-proportional hazards regression model was used to estimate mortality rate ratios and 95% confidence intervals of the combined effects of BMI categorized into three levels (Normal <25; Overweight 25-29.9; Obese \geq 30 kg/m^2), and total PA categorized in tertiles (Low <39; Medium 39-44; High >44 MET-hours/day) on the rate of death from all causes, CVD and cancer.

We adjusted our estimates for age, smoking status and pack-years of smoking, alcohol consumption, educational level, and parental history of cancer or cardiovascular disease as potential confounders. Person-years were calculated from January 1, 1998 until the date of death or August 31, 2007 (for all deaths) or December 31, 2004 (for cardiovascular and cancer death), whichever came first.

A complete case analysis included 27,798 men from the analytic cohort, and 2686 of the total deaths. We evaluated the potential effect of missing values on the

observed results using multiple imputation analyses (Royston, 2004; van Buuren et al, 1999).

In order to reduce the effects of preclinical or chronic illness on the baseline BMI and PA, we next excluded the first three years follow-up ($n=479$), current and former smokers ($n=16,814$), and those men who had lost weight between the age of 20 years ($BMI > 18.5 \text{ kg/m}^2$) and age at baseline ($BMI < 18.5 \text{ kg/m}^2$) ($n=21$). We also excluded heavy manual workers ($n=1369$) since overall mortality from cancer has been found to be significantly higher among men with manual occupations (Rosengren and Wilhelmsen 2004). All of the exclusions left a restricted cohort of 9115 men and 621 total deaths for the analysis. Differences between rate ratios from the analytic cohort and from the restricted cohort in each combination of obesity status and PA level were tested one at a time by comparing the confidence interval associated with the RR of the restricted cohort ($n=9,115$) with the null value (point estimate) of the rate ratios of the analytic cohort ($n=27,798$).

Paper IV

The Cox-proportional hazards model was used to estimate prostate cancer rate ratios and 95% confidence intervals associated with the average adult lifetime (age 30, 50, and current) walking/bicycling duration. For incidence analyses each participant accrued follow-up time from January 1, 1998 until the date of prostate cancer diagnosis, death from any cause, or study end in December 31, 2007 for total or December 31, 2006 for prostate cancer sub-types, whichever came first. For mortality analysis each participant accrued follow-up time from January 1, 1998 until the date of prostate cancer death, death from any cause, or study end in December 31, 2007, whichever came first.

We adjusted for baseline age, waist-to-hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat, and parental history with respect to prostate cancer.

We checked whether the proportional hazard assumption was reasonable in the multivariate models. Scaled Schoenfeld's residuals were regressed against survival time. There was no evidence of departure from the assumption. We examined potential effect modification for the relation between lifetime walking/bicycling and total prostate cancer incidence rate according to baseline age, waist-to-hip ratio and tested the statistical significance of the interactions with the Wald test.

We used piece-wise linear spline (one knot at 30 min/day, most common value) and restricted cubic spline (three knot positions corresponding to quartiles of the observations) Cox regression to flexibly model and graph the multivariable adjusted rate ratio for lifetime walking bicycling levels in predicting prostate cancer incidence and mortality.

A complete case approach reduced the analytic cohort to 31,872 men; 1966 incidence cases and 185 prostate cancer deaths. We evaluated the potential effect of missing values on the observed results using multiple imputation analyses (Royston, 2004; van Buuren et al, 1999).

Statistical analyses and graphs for all papers were performed with Stata®, version 9.2 or later (StataCorp, TX, USA).

Modeling strategies used for physical activity

Regression models specified in their simplest form assume that a certain transformation of the measure of occurrence of the disease (log odds, log incidence or mortality rate) is linearly related to the exposure (i.e. total PA), but this assumption may not be reasonable.

We used two different methods to investigate the shape of the exposure-disease association or to assess whether a postulated shape was correct. The first method involves categorizing the continuous PA variable into categories and then modeling PA using indicator (or dummy) variables. This is a common approach to present results in tabular form.

The second method is based on the construction of piece-wise linear or polynomials of the exposure variable, which is known as linear or restricted cubic splines. A draftsman's spline is a flexible strip of metal or rubber used to draw curves. Splines are piece-wise polynomial functions that can take virtually any shape. The type of spline that is generally most useful is the cubic spline function that is restricted to be smooth at the junction of each cubic polynomial (Harrell, *et al.* 1988). We used restricted cubic spline to model the incidence or mortality rate in survival analysis of paper II, III, and IV.

Imputation of missing data

Missing values are inevitable in the analysis of epidemiological studies. The problems of analyzing incompletely observed data have been extensively studied in statistical literature in recent decades (Rubin and Schenker 1986, Schafer 1999, van Buuren, *et al.* 1999). With the advent of new computational methods and software the practice of filling in missing data with reasonable values has become increasingly attractive in epidemiologic research (see <http://www.multiple-imputation.com> for literature references and software links).

The proportion of missing for each single type of PA ranged from 2 percent for sleeping variable to 9.9 percent for work/occupation. The simple deletion of cases with any missing value on single variables within the PA questionnaire would result in discarding about 20% of the subjects in our study. Non-response on some PA questions was of special concern as summary measures such as total PA, expressed in MET-hours/day, were calculated by means of a sum of variables. Thus, values could be missing for a single activity but complete for others. For instance, a subject with complete information for most type of activities (occupation, household work, walking, inactivity, sleeping) but a missing answer for exercise would result in a missing for the total PA score.

A complete case analysis, discarding observations with no complete information on disease, exposure, and all confounders, is the standard way (default method of statistical software) of dealing with missing data. Concerns are usually manifested as loss of efficiency and biases due to systematic difference between observed and unobserved values. A slightly more advanced approach is to use single imputation, where missing values are simply filled in by a plausible estimate, such as the mean or median or predicted means from a regression model. Even if the missing values could be imputed in such a way subsequent analysis would still fail to account for missing-data uncertainty since imputed values are only estimate of the unknown 'true' values. Any analysis that ignores the uncertainty of missing-data prediction will lead to standard errors that are too small and *P*-values that are artificially low.

Multiple imputation techniques have been proposed as a valid alternative and are increasingly implemented in statistical software packages. Unlike other imputation

methods, multiple imputations produce not one but several imputed datasets. This enables it to appropriately reflect the uncertainty due to missing data and, hence, to produce valid statistical inferences (Rubin 1987).

We used an implementation for Stata of a method of multiple multivariate imputations of missing values developed by Patrick Royston from MRC Clinical Trials Unit, London (Royston 2004). The method is known as MICE, an acronym for Multiple Imputations by Chained Equations (van Buuren, *et al.* 1999). Of note, the Stata implementation of the MICE procedure allows the user to specify an imputation regression model for each variable with missing values (continuous, categorical with two or more levels) in the original dataset. The results of the method are multiple datasets with complete information on both the main exposure (PA) and all potential confounders (Royston 2004). To avoid bias, we always included a variety of predictors (socio-demographic, life-style, anthropometric, history of diseases) in the imputation models including the censoring indicator as well as the survival time (log scale).

This imputation method is based on the assumption that missing data are ignorable as defined by Rubin, either “missing at random” or “missing completely at random” (Rubin 1987). A multiple imputation version of MICE procedure involves repeating this simple imputation step a number of times, and five is enough when the proportion of missing data is not large. The results obtained from multivariable regression models estimated on imputed datasets are then combined, using the rules provided by Rubin to produce overall estimates and standard errors that reflect missing-data uncertainty (Rubin 1987).

4.2 META-ANALYSIS

We performed a dose-response meta-analysis of published epidemiologic studies to summarize the evidence about the association between a specific type of PA, walking, with CHD risk.

4.2.1 Selection of studies

The Medline electronic database was searched to identify relevant studies using a combined text word and MeSH heading search strategy of the terms “physical activity”, “exercise”, “walking”, “cardiovascular disease”, “coronary heart disease”. Reference lists of retrieved articles were scanned for any other relevant studies. Previous systematic reviews including the Report of Surgeon General on physical activity and health were also examined for studies eligible for inclusion (USDHHS 1996). Due to language resource constraints, the search was limited to English-language papers only from 1954 to 2008. A total of 10 prospective cohort studies and 1 randomized control trial study met the inclusion criteria; with 282,661 participants free of CHD at baseline and 4,959 cases at follow-up (Folsom, *et al.* 1997, Hakim, *et al.* 1999, LaCroix, *et al.* 1996, Lee, *et al.* 2001, Manson, *et al.* 2002, Manson, *et al.* 1999, Morris, *et al.* 1990, Paffenbarger, *et al.* 1978, Pereira, *et al.* 1998, Shaper, *et al.* 1991, Tanasescu, *et al.* 2002).

4.2.2 Statistical analysis

The relationship between walking and CHD risk was assessed with random-effects dose-response meta-regression models. We used the method put forward by Greenland and Longnecker as implemented and illustrated by Paper VI to back calculate and pool study-specific trend estimates (Greenland and Longnecker 1992, Orsini, *et al.* 2006).

To use the Greenland and Longnecker method data about relative risk, 95% confidence limits, dose, cases, non-cases (or person-time) for at least three walking categories need to be extrapolated from each publication (Hakim, *et al.* 1999, LaCroix, *et al.* 1996, Lee, *et al.* 2001, Manson, *et al.* 2002, Manson, *et al.* 1999, Morris, *et al.* 1990, Tanasescu, *et al.* 2002).

Three studies (Folsom, *et al.* 1997, Paffenbarger, *et al.* 1978, Pereira, *et al.* 1998) were excluded from the dose-response meta-analysis because walking was classified in only two levels (high versus low). For each study we assigned the median or mean level of walking for each category. When the median or mean walking level per category was not presented in the article, we assigned the midpoint of the upper and lower bounds in each category as the average walking level. If the lower or upper bound was not provided, we assumed that it had the same amplitude as the preceding category.

Given that walking was reported in different ways (MET, pace, time) we first summarized trend estimates separately for each walking measure and then we summarized all trend estimates based on a uniform measure; MET-hours/week.

The variation in trend estimates underlying the different studies (statistical heterogeneity) was evaluated the Cochrane Q statistic (Cochran 1954). The Q statistic is a chi-square test with degrees of freedom equal to the number of studies minus one, and it is commonly used to test the null hypothesis of homogeneity of estimates across studies. A large P -value, saying greater than 5%, means that the Q statistic did not detect any statistically significant heterogeneity across studies.

Furthermore, we also calculated a measure of inconsistency across studies, called I^2 , which represent the proportion of variability in the trend estimates that is due to the between-study variation rather than the within-study error (Higgins and Thompson 2002). Mild heterogeneity was defined as an I^2 of 25%, moderate heterogeneity as an I^2 of 50%, and severe heterogeneity as an I^2 of 75%.

To identify potential effect modifier of the association between walking and CHD risk we performed subgroup analyses by gender, age of the study population, and follow-up duration. To identify potential influential studies and therefore the robustness of the conclusions of the meta-analysis itself we sequentially excluded one study at the time in the estimation of the dose-response meta-regression model.

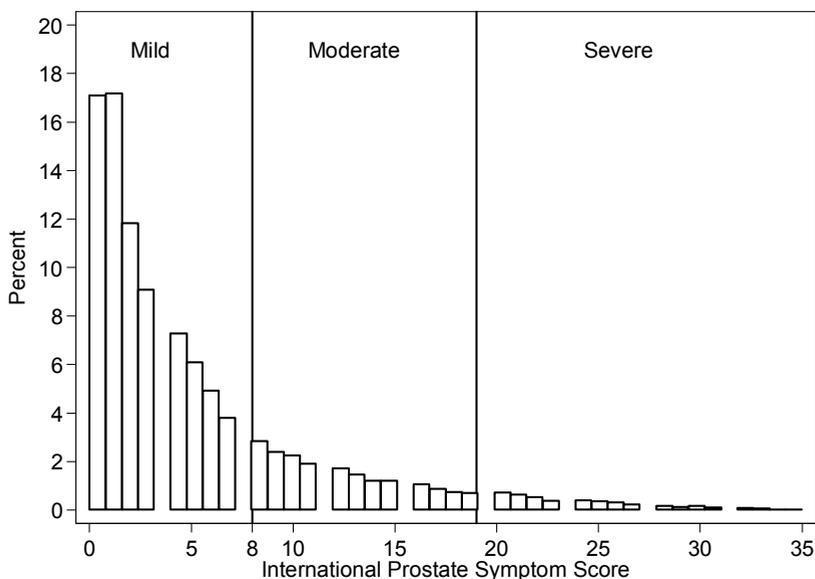
To evaluate publication bias we analyzed the correlation between the magnitude of the trend estimate and its precision as measured by the standard error (or width of the confidence interval) (Sterne, *et al.* 2001). We used the Egger's regression asymmetry test and the funnel plot (Egger, *et al.* 1997). The funnel plot is a scatter between study precision (standard error of the log relative risk) and measure of association (log relative risk). The name "funnel plot" is based on the fact that the precision in the trend estimate will increase as the sample size, in particular the number of cases, of the studies increases. Trend estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence bias, the plot will resemble a symmetrical inverted funnel.

5 RESULTS

5.1 LOWER URINARY TRACT SYMPTOMS (PAPER I)

Figure 5.1 shows the distribution of the IPSS among 30,377 men with complete information about PA and IPSS score, of which 6905 reported moderate to severe LUTS ($IPSS \geq 8$). The prevalence of moderate to severe urinary symptoms increased with age; ranging from 12% among men aged 45-49 years to 41% among men aged 75-79 years.

Figure 5.1 Distribution of the international prostate symptom score in the Cohort of Swedish Men.



We next graphed the crude odds (cases/non-cases) and ratios of odds of having moderate to severe urinary symptoms as a function of baseline total PA levels categorized into quartiles (Figure 5.2). The median values of total PA within each quartile were 36, 39, 43, and 47 MET-hours/day.

The odds of experiencing moderate to severe LUTS significantly decreased with increasing level of total PA; within each quartile the odds were (from lowest to highest) 36%; 29%, 28%, and 25%. Compared to the bottom quartile of total PA (<37.9 MET-hours/day), the crude odds of experiencing moderate to severe urinary symptoms was significantly 30% lower (95% confidence interval (CI) = 25-35%) in the highest quartile (> 45 MET-hours/day). The greatest reduction (20%) in the odds of experiencing moderate to severe LUTS was observed comparing the second quartile vs. the bottom quartile of total PA.

Figure 5.2 Crude odds (cases/non-cases) and ratios of odds (bottom quartile as referent group) of experiencing moderate to severe lower urinary tract symptoms (LUTS) according to quartiles of baseline total physical activity, MET-hours/day.

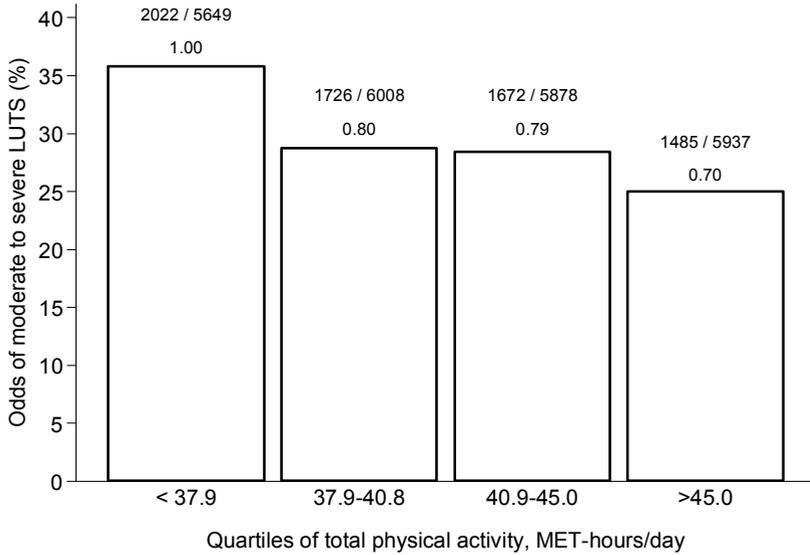
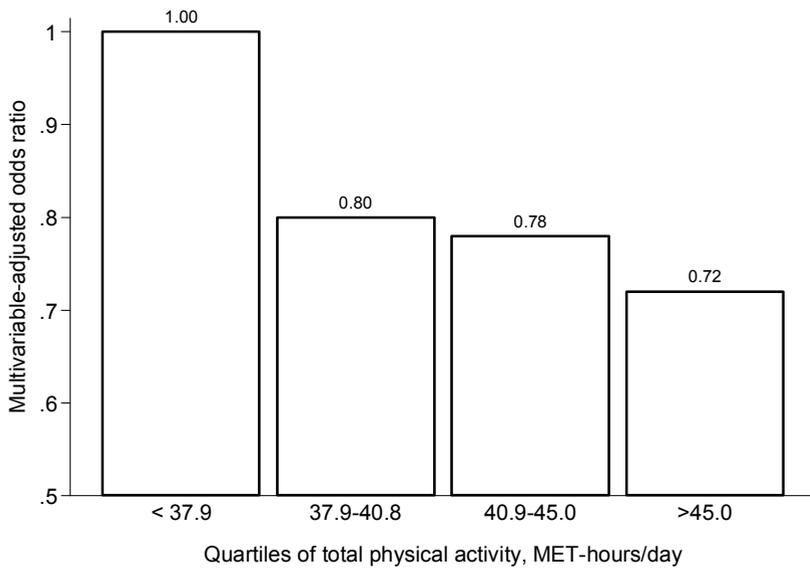


Figure 5.3 Multivariable odds ratios for moderate to severe lower urinary tract symptoms according to quartiles of baseline total physical activity, MET-hours/day.



We next compared the odds of experiencing moderate to severe urinary symptoms controlling for baseline age, an important predictor of LUTS. The age-adjusted odds of experiencing moderate to severe urinary symptoms in the highest quartile of total PA (> 45 MET-hours/day) was 32% lower (95% CI = 27-37%) compared to the lowest quartile (< 37.9 MET-hours/day).

Further adjustment for waist-to-hip ratio, diabetes, alcohol consumption, smoking status, and years of education did not substantially change the estimates (Figure 5.3). The multivariable-adjusted odds of experiencing moderate to severe urinary symptoms in the highest quartile of total PA (> 45 MET-hours/day) was 28% lower (95% CI = 21-34%) compared to the lowest quartile (< 37.9 MET-hours/day).

We also observed a significant inverse association between quartiles of total PA recalled at age 30 years and the odds of moderate to severe LUTS. The multivariable-adjusted odds of experiencing moderate to severe urinary symptoms in the highest quartile of total PA at age 30 years was 12% lower (95% CI = 2-19%) compared to the lowest quartile.

We further also investigated whether the association between baseline total PA and LUTS changed when including those men initially excluded because of missing data on both PA and LUTS (analysis not shown in Paper I). Table 5.1 shows age and multivariable adjusted odds ratios for moderate to severe LUTS according to quartiles of baseline total PA combining estimates derived on five multiply imputed datasets (each of size $n = 45,906$). The magnitude of the odds ratios based on complete-subjects and multiple imputations were overall similar; the average of the relative differences for the multivariable-adjusted odds ratios was 1%.

Table 5.1 Age and multivariable adjusted odds ratio (OR) for moderate to severe lower urinary tract symptoms according to quartiles of baseline total physical activity based on five multiply imputed datasets (each of size $n = 45,906$).

	Quartiles of total physical activity, MET-hours/day			
	< 38	38-41	41-45	≥ 45
Moderate to severe LUTS				
No. of subjects ^a	11,486	11,546	11,410	11,464
No. of cases ^a	3087	2669	2586	2409
Age-adjusted OR (95% CI) ^b	1.00	0.82 (0.77-0.88)	0.76 (0.70-0.82)	0.68 (0.64-0.73)
Multivariable OR (95% CI) ^b	1.00	0.84 (0.78-0.89)	0.78 (0.72-0.84)	0.71 (0.66-0.77)

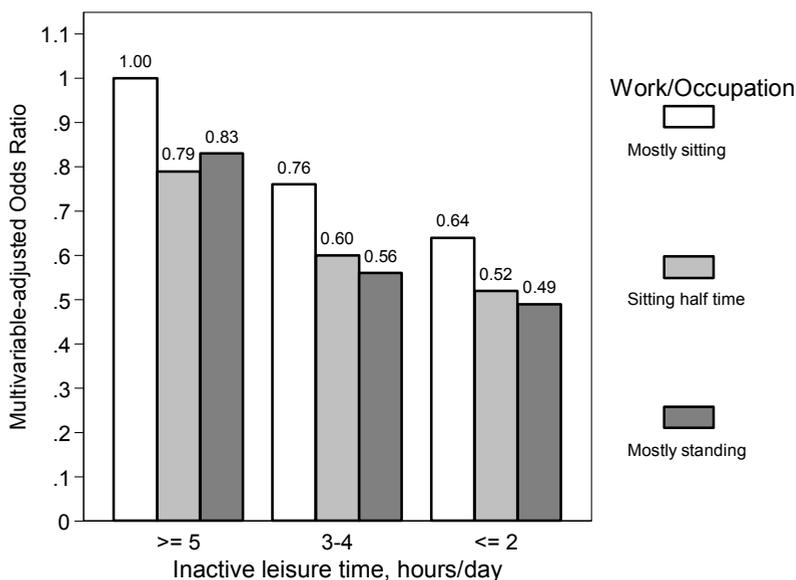
^a Number of subjects and cases are from the first imputed dataset.

^b Odds ratios were combined across five datasets obtained by multiple imputation using the Rubin's method (Rubin 1987).

Our next goal was to examine the combined effect of inactive leisure-time (watching TV/reading, hours/day) and type of work/occupational activity in predicting the odds of having moderate to severe LUTS (Figure 5.4). The odds of experiencing moderate to severe LUTS decreased with decreasing levels of inactivity (hours/day watching TV/reading) within each work/occupational activity from mostly sitting to mostly standing. There was no evidence of significant interaction between inactive leisure-time and type occupational activity in predicting odds of moderate to severe LUTS (P for interaction = 0.90).

Those men who had 2 hours/day or less of inactive leisure-time were less likely (about 36% risk reduction) to experience moderate to severe LUTS as compared to 5 hours/day or more, adjusting for occupational activity. Those men who were highly active at work (mostly standing) were less likely (about 25% risk reduction) to experience moderate to severe LUTS as compared to those men who were mostly sitting, adjusting for inactivity levels.

Figure 5.4 Multivariable adjusted odds ratios for moderate to severe lower urinary tract symptoms according to combined categories of baseline work/occupation and inactive leisure-time.



Finally, we assessed the combined effect of distant (at age 30 years) and current PA levels in predicting the odds of having moderate to severe LUTS. The risk of LUTS for those men who were highly inactive (5 hours/day or more) both at age 30 years and at current age was 2 fold (OR=1.90, 95% CI=1.41-2.59) the risk of those men who were 2 or less hours/day inactive at both ages.

Compared to less active men (walked or biked 40-60 min/day or less and exercised less than 4 hours/week) both in the distant and recent past, the odds of moderate to severe LUTS decreased by 22% (95% CI = 14-30%) for more active men (walked or biked ≥ 60 min/day and exercised ≥ 4 hours/week).

5.2 OVERALL CANCER INCIDENCE, MORTALITY, AND SURVIVAL (PAPER II)

During an average follow-up of 7 years, we identified a total of 3714 newly diagnosed cancers and 1153 cancer deaths from all sites.

We first investigated the association between total PA and cancer incidence. The age-adjusted incidence rate ratio for every 4 MET-hours/day increment of total PA, which is approximately equivalent to 1 hour of moderate effort, was 0.96 (95% CI=0.93-1.00). Further adjustment for BMI, smoking and pack-years, alcohol consumption, educational level, history of diabetes, and parental history of cancer slightly attenuated the trend estimate. Figure 5.5 shows the multivariable incidence rate ratio for cancer in all sites according to total PA. The referent total PA score was 30 MET-hours/day. The multivariable incidence rate for cancer from all sites linearly decreased by 2% for every 4 MET-hours/day increment, although this change was not statistically significant (95% CI = 0.94-1.01). The test for interaction did not detect any evidence of effect modification by smoking ($P=0.83$).

We next examined the association between total PA and cancer mortality. The age-adjusted mortality RR for every 4 MET-hours/day increment of total PA was 0.86 (95% CI = 0.80-0.92). Further adjustment for BMI, smoking, alcohol, education, diabetes, and parental history of cancer did not substantially change the trend estimate. Figure 5.6 shows the multivariable mortality rate ratio for cancer in all sites according to total PA. The multivariable mortality rate for cancer in all sites linearly decreased by 12% for every 4 MET-hours/day increment of total PA (95% CI = 0.82-0.94). The test for interaction did not detect any evidence of effect modification by smoking ($P=0.48$).

We next examined survival after cancer diagnosis among 2551 men with complete information on PA and potential confounders, 598 of which subsequently died due to cancer. Compared to the referent value of 40 MET-hours/day (median total PA score among cancer survivors), the mortality rate from cancer significantly and linearly decreased by 17% (95% CI = 4 - 28%) for every increment of 4 MET-hours/day in the range 40 to 54 MET-hours/day. No change in the mortality rate was observed below the median value of total PA (Figure 5.7).

As shown in Figure 5.8 men in the top quartile of total PA experienced consistently higher cancer survival (Rate ratio=0.69; 95% CI = 0.53-0.89) compared to those men in the lowest quartile throughout follow-up. The 5-year survival for cancer was 77% for men who engaged in high levels of total PA (top quartile, > 43 MET-hours/day), which was significantly higher than 70% for medium (interquartile range, 38-43 MET-hours/day) activity levels and 69% for low (bottom quartile, < 38 MET-hours/day) activity levels.

In our final analysis we focused on walking/bicycling, the main component of active living, in relation to cancer incidence, mortality and survival after cancer diagnosis. Compared to men who hardly ever walked or biked, the cancer incidence rate associated with walking/bicycling an average of 60 to 90 min/day decreased significantly by 16% (95% CI=2-28%). The cancer mortality rate associated with walking/bicycling an average of 30 min/day was 34% lower (95% CI = 18-47%) in the analytic cohort and 33% lower (95% CI = 14-47%) in cancer survivors compared to men who hardly ever walked or biked.

Figure 5.5 Multivariate incidence rate ratios for cancer in all sites according to total physical activity, expressed by MET-hours/day. Solid line represents linear trend and long dash line represents restricted cubic spline. Dotted lines represent 95 confidence limits for the linear trend.

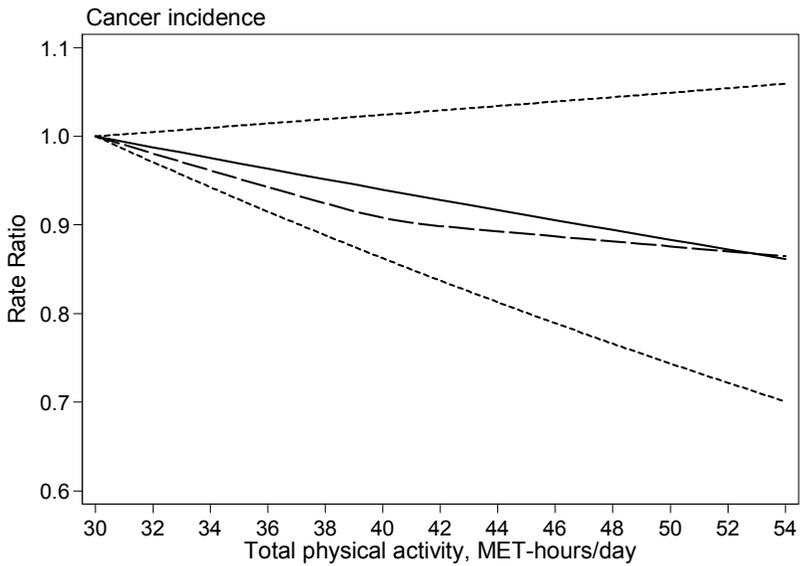


Figure 5.6 Multivariable mortality rate ratios for cancer in all sites according to total physical activity expressed by MET-hours/day. Solid line represents linear trend and long dash line represents restricted cubic spline. Dotted lines represent 95 confidence limits for the linear trend.

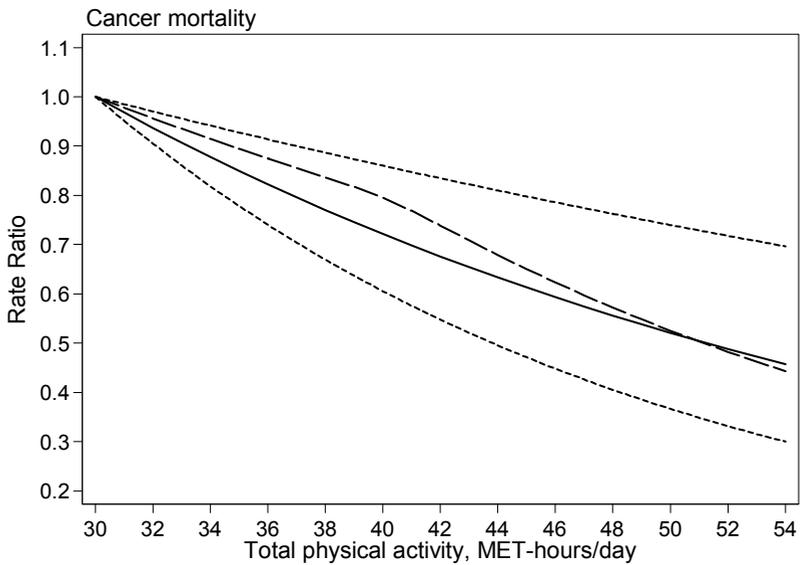


Figure 5.7 Multivariable mortality rate ratios for cancer in all sites according to total physical activity expressed by MET-hours/day. Solid line represents linear trend and long dash line represents restricted cubic spline. Dotted lines represent 95 confidence limits for the linear trend.

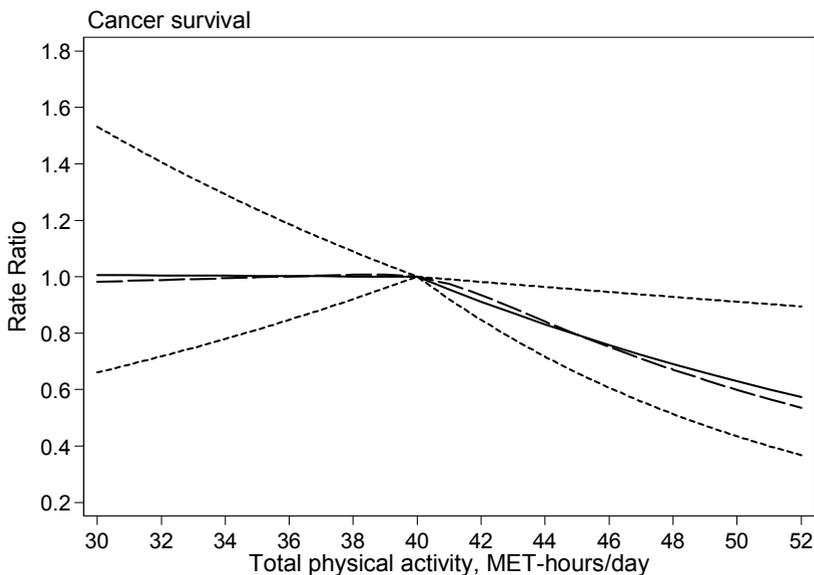
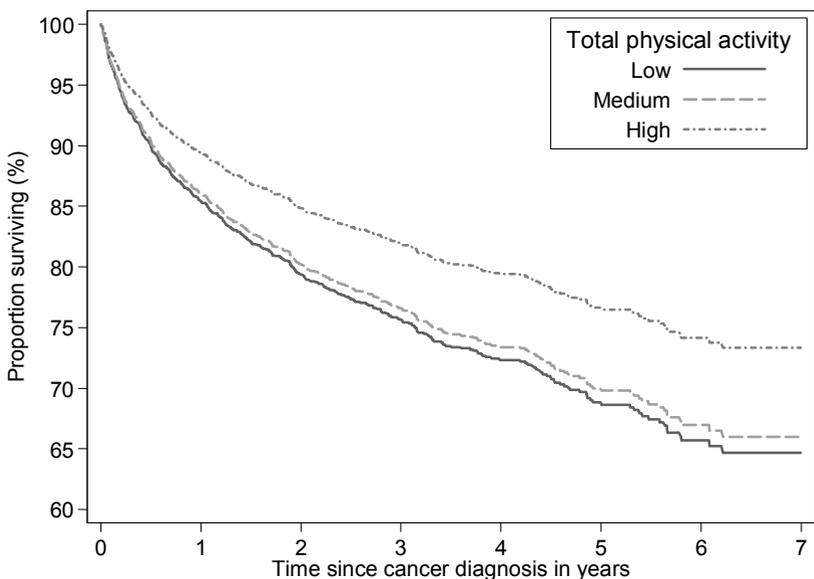


Figure 5.8 Cumulative survivor function according to levels of total physical activity (Low=Bottom quartile; Medium=Interquartile range; High=Top quartile).



5.3 OVERALL AND CAUSE-SPECIFIC MORTALITY (PAPER III)

During 9.7 years of follow-up we identified 4086 deaths among 37,633 men 45 to 79 years of age at baseline from the COSM. We were interested in estimating and comparing mortality rates (all causes, cardiovascular, and cancer) according to categories of BMI (normal, overweight, and obese) and total PA tertiles (Low, median = 37; Medium, median = 41; and High, median=47 MET-hours/day).

Figure 5.9 shows the age-adjusted mortality rate ratios from all causes estimated using the normal weight and the highest tertile of total PA as referent group. Obesity predicts an increase in mortality rates from all causes regardless of the PA level. Men in the lowest level of total PA tended to have higher death rates compared with men in the highest level. Obesity (BMI \geq 30 kg/m²) was associated with a significant 36% higher (95% CI = 19-55%) mortality rate from all cause compared to normal weight (BMI < 25 kg/m²), adjusting for total PA levels and age. Low levels of total PA (bottom tertile) were associated with a significant 36% higher (95% CI = 24-50%) mortality rate from all cause, adjusting for BMI and age.

Figure 5.9 Age-adjusted mortality rate ratios for death from all causes according to joint categories of body mass index and tertiles of total physical activity.

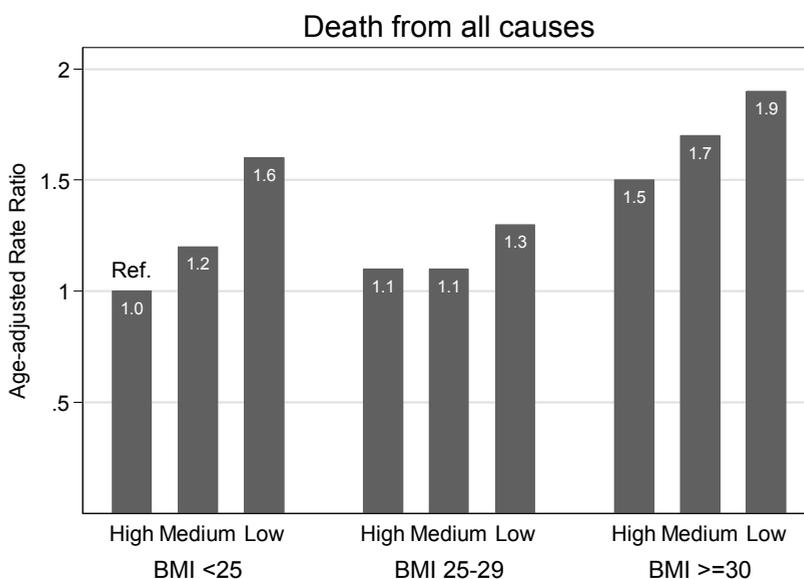


Figure 5.10 shows the age-adjusted mortality rate ratios from CVD estimated using again the normal weight and the highest tertile of total PA as referent group. Obesity was associated with a significant 63% higher (95% CI = 27-110%) mortality rate from CVD compared to normal weight, adjusting for total PA and age. Low levels of total PA were associated with a significant 42% higher (95% CI = 18-71%) mortality rate from CVD, adjusting for BMI and age.

Figure 5.10 Age-adjusted mortality rate ratios for death from cardiovascular disease according to joint categories of body mass index and tertiles of total physical activity.

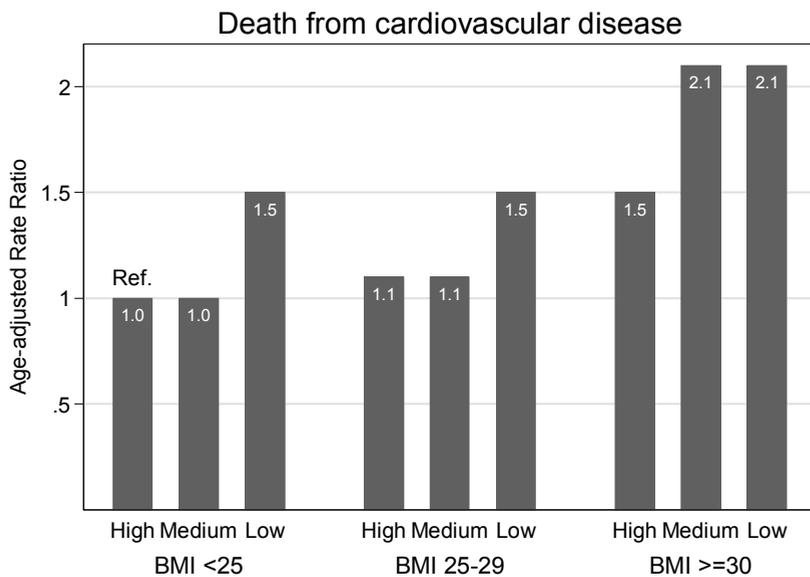


Figure 5.11 Age-adjusted mortality rate ratios for death from cancer according to joint categories of body mass index and tertiles of total physical activity.

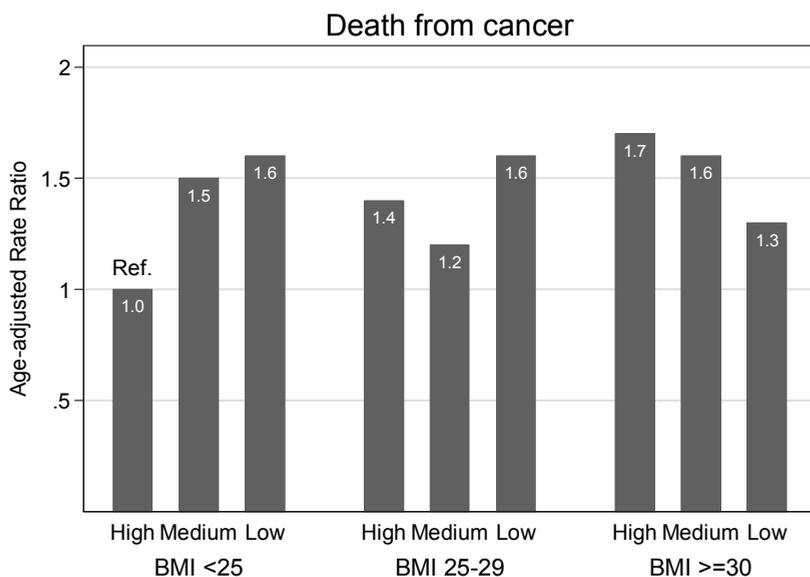


Figure 5.11 shows the age-adjusted mortality rate ratios from all cancers estimated using the normal weight and the highest tertile of total PA as referent group. The cancer mortality rate tended to increase with BMI only among men in the highest level of total PA. Probably related to the limited number of cases, no clear pattern in cancer mortality rates was observed for obesity among men in the medium and low PA level. Low levels of total PA were associated with a significant 27% higher (95% CI = 4-55%) mortality rate from cancer, adjusting for BMI and age.

Further adjustment for smoking status and pack-years, alcohol consumption, educational level, and parental history of cancer or CVD, slightly attenuated the age-adjusted rate ratios. The average relative difference comparing age and multivariable-adjusted rate ratios was -1.4% (range from -5% to 5%) for mortality from all causes.

Figure 5.12 shows the multivariable-adjusted rate ratios for mortality from all causes estimated on complete-subjects and multiple imputed datasets. The magnitude as well as the direction of the rate ratios based on complete data and multiple imputation analyses were very similar overall; the average of the relative differences was 4% (range from 1% to 12%) for all causes of death. Compared to men who were lean and active the multivariable adjusted rate ratios of death from all causes were 1.44 (95% CI=1.11-1.86) for obese-active men, 1.54 (95% CI=1.34-1.77) for lean but inactive men, and 1.81 (95% CI=1.48-2.23) for obese-inactive men.

To examine the possibility that preclinical symptoms of cancer, CVD or other disease might have affected BMI and/or PA habits, thereby biasing our results, we examined the combined effects of BMI and PA (based on complete data) in predicting mortality in a restricted cohort of 9115 men after excluding the first three years of follow-up, current and former smokers, those men who had lost weight from age 20 to baseline, and heavy manual workers.

Comparing the restricted cohort ($n=9115$; mean age = 59.1 years; mean total PA level = 40.6 MET-hours/day; mean BMI = 25.3 kg/m²) with the analytic cohort ($n=27,798$; mean = 58.6 years; mean total PA = 41.7 MET-hours/day; mean BMI = 25.6 kg/m²) or the study population ($n=37,633$; mean age = 58.9 years; mean total PA level = 41.7 MET-hours/day; mean BMI = 25.6 kg/m²) there were negligible differences. Overall, the mortality rate ratios associated with BMI and PA levels were overall significantly higher in the restricted cohort (Figure 5.13). The average underestimation of the rate ratios in the analytic cohort was about -27% (range from -18% to -36%) for mortality from all causes.

The mortality rate from all causes were 1.65 (95% CI=1.20-2.27) for overweight-to-obese and active men, 2.15 (95% CI=1.59-2.91) for lean-inactive men, and 2.04 (95% CI=1.52-2.74) for overweight-to-obese and inactive men compared to lean-active men. The mortality rate from CVD among normal weight and inactive men was 60% higher (95% CI=0.84-3.05) compared to normal weight active men, although this increase was not significant. The mortality rate from cancer among normal weight and inactive men was 2.5 times greater (95% CI=1.20-5.12) compared to normal-weight active men. The Wald tests for interaction between BMI and PA in predicting mortality were not statistically significant ($P = 0.10$ for death from all causes, $P = 0.74$ for death from CVD, $P = 0.23$ for death from cancer).

Figure 5.12 Multivariable-adjusted mortality rate ratios for death from all causes according to joint categories of body mass index and tertiles of total physical activity based on complete data and multiple imputation analyses.

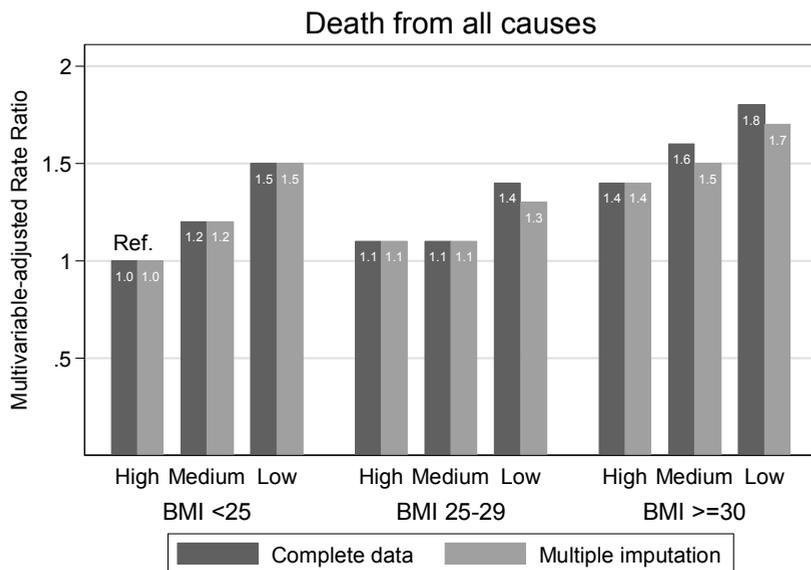
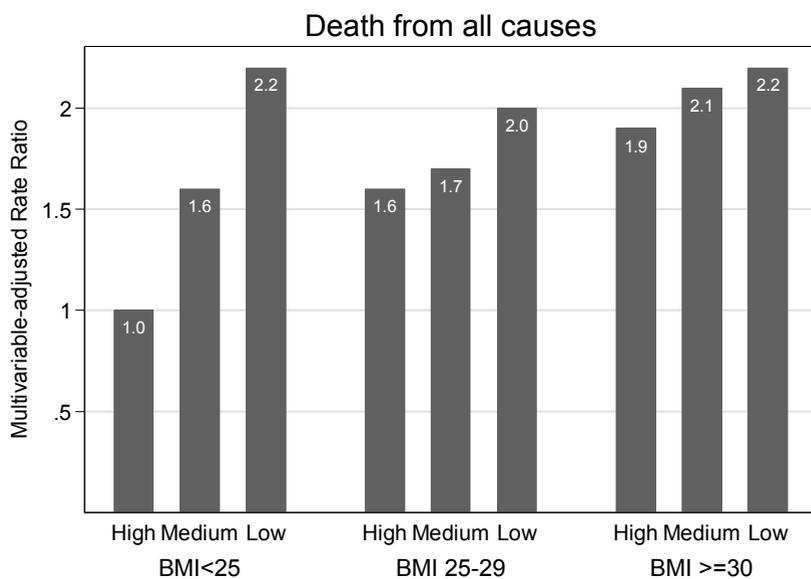


Figure 5.13 Multivariable-adjusted mortality rate ratios for death from all causes according to joint categories of body mass index and tertiles of total physical activity after exclusion of the first three years of follow-up, current and former smokers, those men who had lost weight from age 20 to baseline, and heavy manual workers.

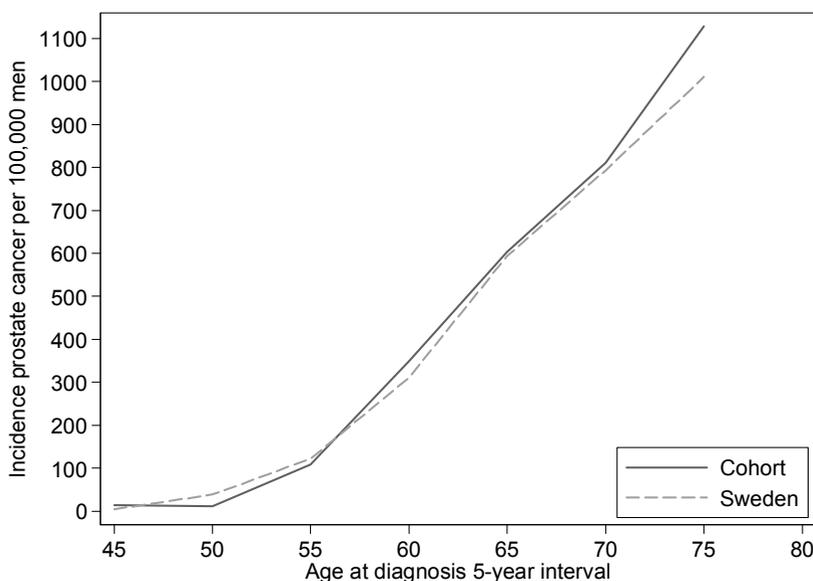


5.4 PROSTATE CANCER INCIDENCE (PAPER IV)

During 10 years of follow-up from January 1, 1998 through December 31, 2007, we documented 2735 newly diagnosed cases of prostate cancer; 1098 of them were classified as localized cancer while 970 were identified as advanced (follow-up through December 31, 2006). Prostate cancer cases had an average of 66 years at baseline and an average of 72 years at diagnosis. The majority of the cases (80%) were diagnosed because of clinical symptoms followed by health check-ups.

As shown graphically in Figure 5.14 for the year 1998, the incidence rate of prostate cancer increases with age, with similar trend in the COSM and the Swedish population.

Figure 5.14 Incidence of prostate cancer in 1998 in the Cohort of Swedish Men and the Swedish population according to 5-year intervals.



We examined the associations between adult lifetime average walking/bicycling duration as continuous variable and incidence and mortality prostate cancer rates. Age-adjusted and multivariable adjusted rate ratios for total, advanced, localized, and fatal prostate cancer according to an increment of 30 min/day (linear trend) of walking/bicycling below and above the referent value of 30 min/day are shown in Table 5.2.

Compared with men who walked or biked 30 min/day, the age-adjusted rate ratio for total prostate cancer linearly decreased by 5% for every 30 min/day increment in the range 30 to 120 min/day. Further adjustment for waist-to-hip ratio, height, history of diabetes, alcohol consumption, smoking status, educational level, total energy intake, consumption of dairy products and red meat, and parental history of prostate cancer did not substantially change the trend estimates. Compared with men who walked or biked at the referent value of 30 min/day, the multivariable-adjusted rate ratio for total prostate cancer linearly decreased by 8% for every 30 min/day increment in the range 30 to 120 min/day. No statistically significant trend was observed in the incidence of

total prostate cancer rate below the lifetime average walking/bicycling of 30 min/day (Figure 5.15). The incidence rate for total prostate cancer associated with the highest lifetime walking/bicycling average of 120 min/day decreased significantly by 17% (95% CI = 1-32%) compared with those men who hardly ever walked or biked.

The trend estimates based on complete-subjects and multiple imputation analyses were overall similar. Compared with men who walked or biked at the referent value of 30 min/day, the multivariable-adjusted rate ratio based on 5 imputed datasets for total prostate cancer linearly decreased by 6% (95% CI= 1-10%) for every 30 min/day increment in the range 30 to 120 min/day.

Table 5.2 Age-adjusted and multivariable adjusted rate ratio (RR) for total, advanced, localized, and fatal prostate cancer according to an increment of 30 min/day of walking/bicycling below and above the referent value of 30 min/day.

	Lifetime walking/bicycling trend for 30 min/day increment	
	< 30	> 30
Total incidence prostate cancer		
Age-adjusted RR (95% CI)	0.94 (0.81-1.09)	0.95 (0.90-0.99)
Multivariate RR (95% CI)	0.94 (0.79-1.11)	0.92 (0.87-0.98)
Localized		
Age-adjusted RR (95% CI)	0.82 (0.65-1.04)	0.91 (0.84-0.99)
Multivariate RR (95% CI)	0.79 (0.60-1.04)	0.91 (0.83-1.00)
Advanced		
Age-adjusted RR (95% CI)	1.14 (0.89-1.46)	0.93 (0.86-1.02)
Multivariate RR (95% CI)	1.12 (0.84-1.49)	0.88 (0.79-0.97)
Fatal prostate cancer		
Age-adjusted RR (95% CI)	1.52 (0.85-2.71)	1.00 (0.83-1.21)
Multivariate RR (95% CI)	1.31 (0.66-2.61)	0.87 (0.69-1.10)

Regarding prostate cancer subtypes, compared with men who walked or biked a lifetime average of 30 min/day, the multivariable-adjusted rate ratio for localized prostate cancer linearly decreased by a marginally significant 9% (95% CI = 0-17%) for every 30 min/day increment of lifetime average walking/bicycling in the range 30 to 120 min/day. The multivariable-adjusted rate ratio for advanced prostate cancer linearly decreased by 12% (95% CI = 3-21%) for every 30 min/day increment in the range 30 to 120 min/day.

For fatal prostate cancer, apart from the greater uncertainty of the estimates due to the smaller number of cases, the results were similar to those for advanced prostate cancer incidence (Figure 5.16). Compared with men who walked or biked a lifetime average of 30 min/day, the multivariable-adjusted rate ratio for fatal prostate cancer linearly decreased by a non-significant 13% for every 30 min/day increment of lifetime average walking/bicycling in the range 30 to 120 min/day. The fatal prostate cancer rate among those men who hardly ever walked or biked increased two-folds (95% CI = 0.95-4.13) compared with men in the highest average lifetime walking/bicycling of 120 min/day, although this increased rate was not significant.

Next, we examined the combined effect of current and distant past (average of age 30 and 50 years) average walking/bicycling duration in predicting prostate cancer risk. Compared with men who walked or biked 20-40 min/day both in the recent past and in the distant past, the lifetime average walking/bicycling more than 60 min/day

Figure 5.15 Multivariable rate ratio for lifetime average walking/bicycling duration (average of age 30, 50 and baseline age) as predictor of total prostate cancer rates. Piecewise-linear spline (solid line with a knot at the referent value of 30 minutes/day) was overlaid with the restricted cubic splines (long dash line).

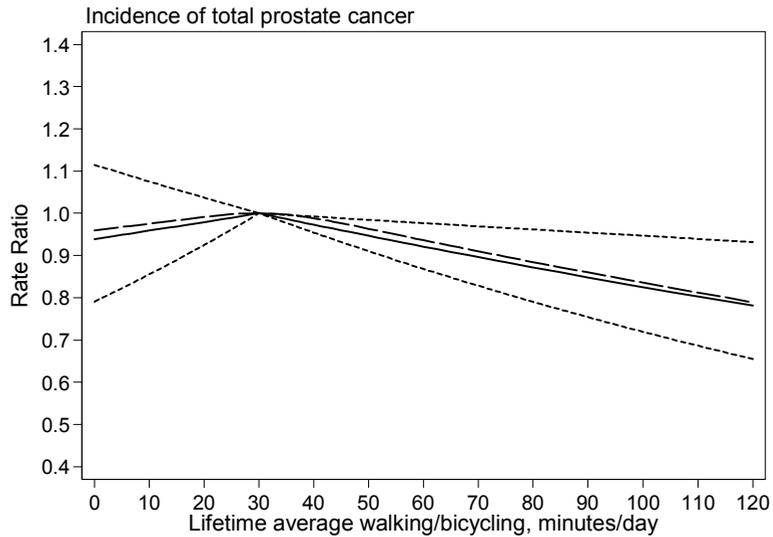
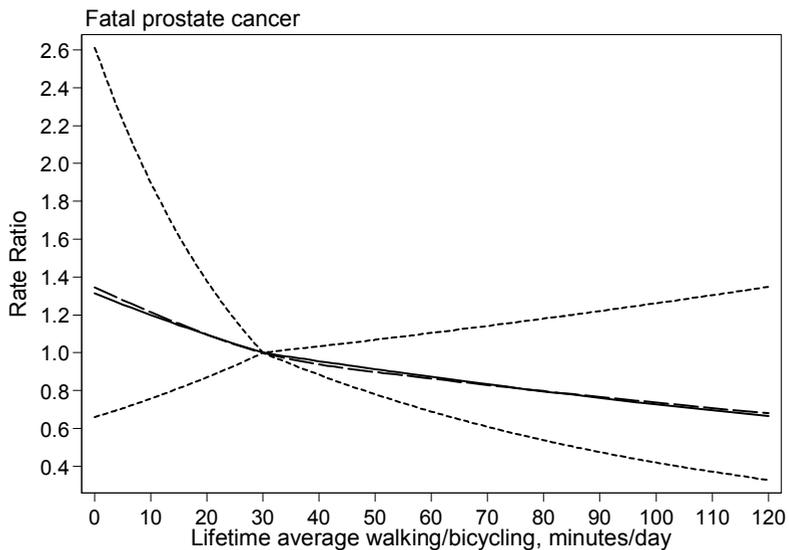


Figure 5.16 Multivariable rate ratio for lifetime average walking/bicycling duration (average of age 30, 50 and baseline age) as predictor of total prostate cancer rates. Piecewise-linear spline (solid line with a knot at the referent value of 30 minutes/day) was overlaid with the restricted cubic splines (long dash line).



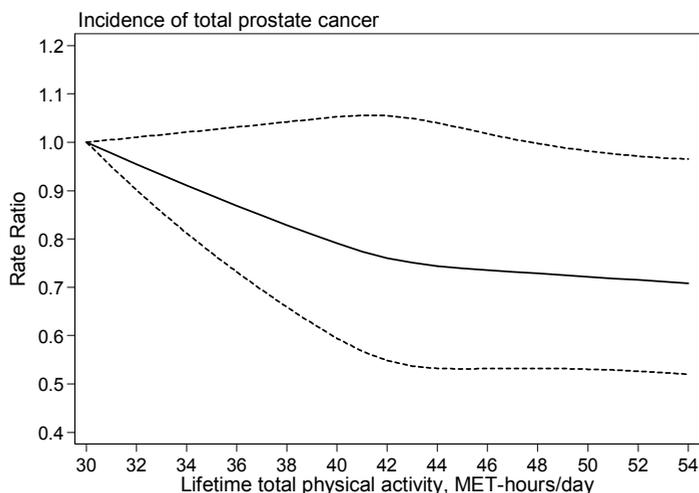
was associated with a marginally significant 15% reduction of total prostate cancer and a significant 27% reduction of advanced prostate cancer risk.

Table 5.3 Age-adjusted and multivariate incidence rate ratio (RR) for total prostate cancer according to quartiles of lifetime total physical activity.

	Quartiles of lifetime total physical activity, MET-hours/day			
	< 38	38-41	41-45	≥ 45
Total prostate cancer				
No. of cases	561	604	609	610
Age-adjusted RR	1.00	0.93	0.90	0.89
(95% CI)		(0.83-1.04)	(0.81-1.01)	(0.79- 1.00)
Multivariate RR	1.00	0.87	0.87	0.82
(95% CI)		(0.77- 0.99)	(0.77-1.00)	(0.72-0.95)

Finally, we assessed the association between the average adult lifetime total PA (age 30, 50, and current) and incidence of prostate cancer (analysis not shown in Paper IV). Age-adjusted and multivariate-adjusted total prostate cancer incidence rate ratios according to quartile of lifetime total PA are shown in Table 5.3. The lifetime total PA showed a statistically significant inverse association with incidence rates of total prostate cancer (Figure 5.17). The age-adjusted rate ratio for the top quartile of lifetime total PA was associated with 11% lower risk of total prostate cancer compared with the bottom quartile. Further adjustment for waist-to-hip ratio, height, history of diabetes, alcohol consumption, smoking status, educational level, total energy intake, consumption of dairy product and meat, and parental history of prostate cancer slightly increased the estimate; the incidence rate ratio in the top quartile of PA decreased by 18% (95% CI=5-28%) in comparison to the bottom quartile.

Figure 5.17 Multivariable-adjusted incidence rate ratios for total prostate cancer according to lifetime total physical activity expressed by MET-hours/day.



5.5 CORONARY HEART DISEASE (PAPER V)

As our focus was on dose-response between walking and CHD risk reduction, we included eight observational studies reporting relative risks of walking in at least three levels (Hakim, *et al.* 1999, LaCroix, *et al.* 1996, Lee, *et al.* 2001, Manson, *et al.* 2002, Manson, *et al.* 1999, Morris, *et al.* 1990, Tanasescu, *et al.* 2002). The majority of the studies showed a decrease in CHD risk associated with high-level walking as compared to low-level walking.

We first examined the dose-response relationship between walking and CHD risk separately according to the type of measure: MET-hours/week (Manson, *et al.* 2002, Manson, *et al.* 1999, Tanasescu, *et al.* 2002), pace (Lee, *et al.* 2001, Manson, *et al.* 1999, Morris, *et al.* 1990, Tanasescu, *et al.* 2002), and time (LaCroix, *et al.* 1996, Lee, *et al.* 2001, Morris, *et al.* 1990, Shaper, *et al.* 1991). The CHD risk decreased by 11% (95% CI = 4-18%) for every increment of 8 MET-hours/week with no evidence of heterogeneity across studies ($Q=3.16$, P -heterogeneity = 0.21; $I^2=37\%$). An increment of 8 MET-hours/week is approximately equivalent to 2.5 hours/week, or 30 min/day on 5 days a week, of moderate-intensity walking. Regarding walking pace, every increment of 2 kilometers per hour was associated with 21% reduced risk of CHD (95% CI = 15-27%; $Q = 1.79$, P -heterogeneity = 0.62; $I^2=0\%$). An increment of 3.5 hours per week (about 30 minutes per day) of walking was significantly associated with 32% CHD risk reduction (95% CI = 11-48%) and no evidence of heterogeneity was found in the study-specific estimates ($Q=2.38$, P -heterogeneity = 0.30; $I^2=16\%$).

We then investigated the dose-response relationship between walking and CHD risk by pooling the eight studies together transforming all the different type of walking measures in a uniform measure expressed in MET-hours/week.

Every increment of 8 MET-hours/week was associated with a statistically significant 19% lower (95% CI = 14-23%) CHD risk. There was no statistically significant heterogeneity across studies ($Q=5.81$, P -heterogeneity=0.56; $I^2=0\%$). The linear trend estimate corresponding to an increment of 8 MET-hours/week is presented in Figure 5.18. We also assessed non-linearity by estimating a quadratic meta-regression model and we found no evidence of better fit of the relative risk estimates as compared to the simpler linear model ($P=0.65$).

In a sensitivity analysis iteratively removing each study from the overall analysis, the CHD risk reduction associated with an increment of 8 MET-hours/week ranged from 20% with the exclusion of the Manson study (Manson, *et al.* 2002) to 18% with removal of Lee data (Lee, *et al.* 2001). Moreover, to assess whether the three studies (Folsom, *et al.* 1997, Paffenbarger, *et al.* 1978, Pereira, *et al.* 1998) reporting only two walking levels (comparing high vs. low walking category) could affect the dose-response meta-analysis we included them into the summary of the specific-study trend estimates but the pooled trend did not changed; the CHD risk did not sign reduce any further namely staying at 19% (95% CI = 15-24%; $Q=10.75$, P -heterogeneity=0.46; $I^2=0\%$).

To evaluate whether the dose-response relationship varied across levels of study characteristics we conducted subgroup analyses and we found no evidence of heterogeneity between subgroups of studies defined by original walking measure ($P=0.50$), gender ($P=0.67$), age of the study population ($P=0.52$), and follow-up duration ($P=0.77$). Overall, the sensitivity analysis suggested that the effect of walking in reducing CHD risk was consistent across study types and methods of analysis.

There was no evidence of publication bias based on the Funnel plot (Figure 5.19), where the horizontal line indicates the pooled trend estimate and the dashed lines the 95% confidence limits. The Egger's regression asymmetry test ($P=0.59$) did not detect evidence of publication bias in the summary of study-specific estimates.

Figure 5.18 Inverse linear dose-response gradient between various measures of walking converted to a uniform measure (MET-hours/week) and risk of coronary heart disease based on a meta-analysis of eight studies.

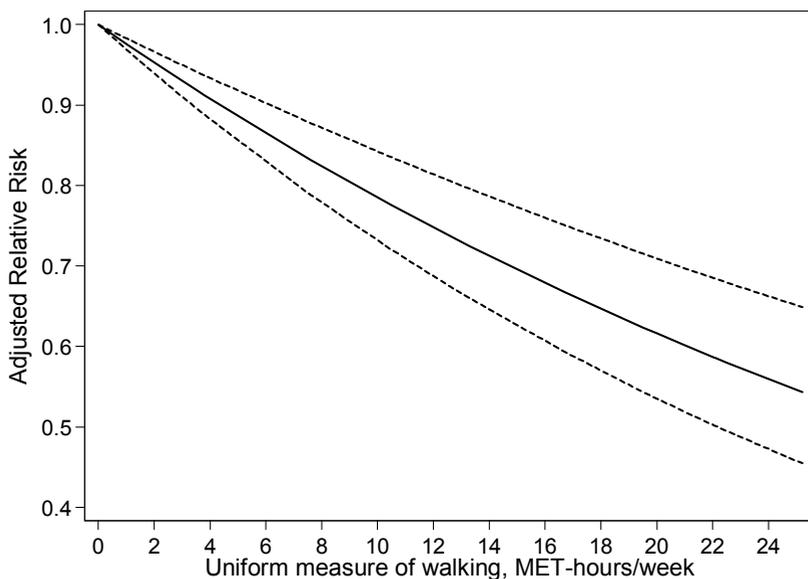
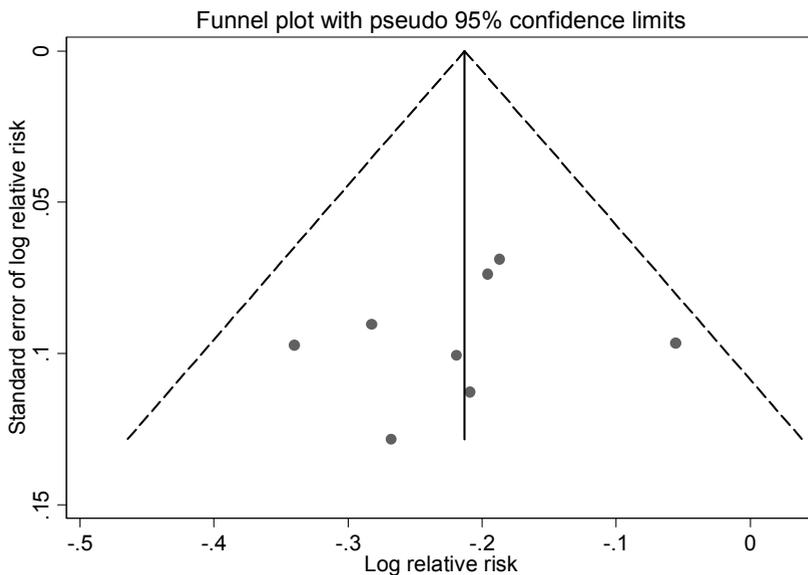


Figure 5.19 Scatter plot between precision (standard error) and linear trend estimate (log relative risk for increments of 8 MET-hours/week) in a meta-analysis of eight studies relating walking to coronary heart disease risk.



5.6 METHODOLOGICAL PAPERS (PAPER VI-VII)

Paper VI and VII contain a description of two user-friendly programs useful among epidemiologists and public health researchers: dose-response meta-analysis (**glst**) and sensitivity analysis for biases in observational studies (**episens**). These two programs are written for Stata® (StataCorp, College Station, TX, USA), a common statistical package among epidemiologists and public health researchers. They are freely downloadable from the Statistical Software Components archive, hosted by Boston College (USA), which is the largest collection of user-written Stata programs (more than 1,000 items downloaded about 77,000 times during the last 12 months) for data manipulation, statistics, and graphics.

Dose-response meta-analysis

Quantitative reviews are expected to include an assessment of the relationship between exposure levels and risk of disease. The standard approach to trend estimation in dose-response meta-analysis when only published category-specific relative risks and their confidence intervals are available, is to fit a linear regression where the response variable is the log relative risk, the assigned dose is the covariate, and the log relative risks are weighted by the inverse of their standard errors. This method is known as inverse variance-weighted least-squares regression, and it assumes that the exposure-specific log relative risks are independent.

It has been shown that assuming independence (zero correlation) among a series of log relative risks estimated using a common referent group will tend to underestimate the variance of the linear trend. Therefore, Greenland and Longnecker proposed a method to back calculate cell counts corresponding to the adjusted relative risks; to estimate the correlations among relative risks; and to incorporate them into the estimation of the dose-response regression model (Greenland and Longnecker 1992).

Since June 1992, when the Greenland and Longnecker paper was published on American Journal of Epidemiology, it has been cited 151 times (through October 2008), of which 50% occurred during the last three years (Data source: ISI web of science). Figure 5.20 shows the percentage and number of citations of the Greenland and Longnecker paper from 1992 to 2008. The two institutions most citing the Greenland and Longnecker paper are Karolinska Institutet (our group) and Harvard University.

Paper VI presents the methods and formulas, regression models, and motivating examples for meta-analysis of different type of epidemiological dose-response data (case-control, cumulative incidence, and incidence rate data). Of note, the formulas for the variances of the log relative risks for incidence rate and cumulative incidence data fix two errors in the Greenland and Longnecker paper (page 1304 second paragraph), which are correct only if the exposure has two levels, but otherwise overestimate the variances.

Online access to the latest updates, presentations at conferences, worked examples, and a list of 27 publications that already used and/or cited Paper VI (Orsini, *et al.* 2006) is available at <http://nicolaorsini.altervista.org/stata/tutorial/glst.htm>.

To illustrate how the **glst** Stata command can be useful to back calculate the dose-response trend in a given summarized data we apply the method to the association between total PA categorized in quartiles and cancer mortality rates in the COSM (Paper II).

Figure 5.20 Percentage and number of citations of the Greenland and Longnecker paper from 1992 to 2008.

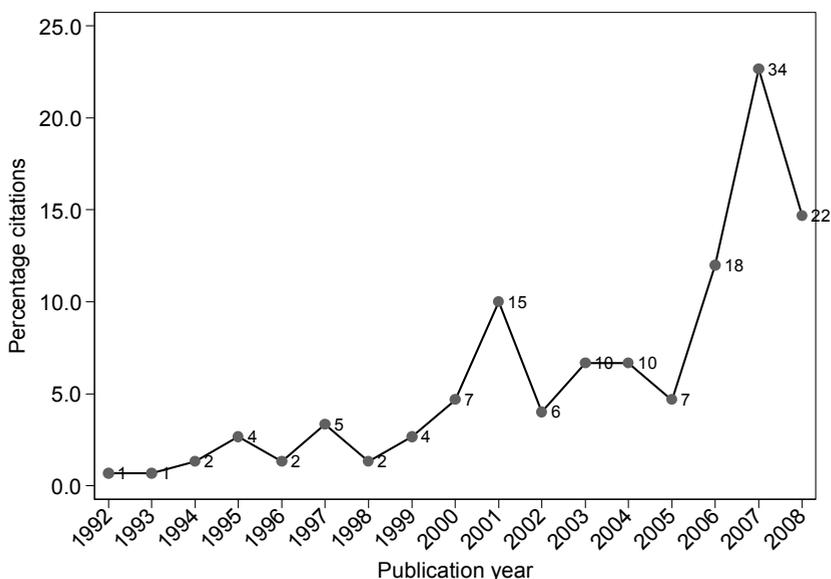


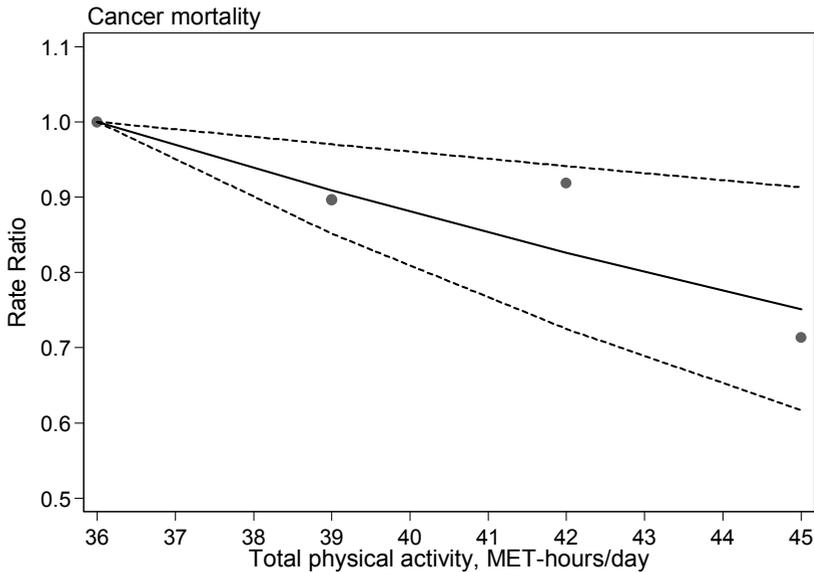
Table 5.4 shows the information required to back calculate the dose-response relationship from published data: dose value, relative risk, 95% confidence limit, cases, and total subjects (or number of person-years) for each quartile of total PA.

Table 5.4 Summarized data about the association between quartiles of total physical activity, expressed in MET-hours/day, and cancer mortality rates in the Cohort of Swedish Men.

Quartile of total activity	Median dose	Adjusted rate ratio	95% Confidence limit		Cases	Total subjects	Person-years
<38	36	1.00	1.00	1.00	217	7,662	68,322
38-40	39	0.90	0.73	1.10	181	7,663	70,536
40-43	42	0.92	0.75	1.12	197	7,663	70,107
>43	45	0.71	0.58	0.88	184	7,662	69,996

To model the mortality rate as a function of total PA we estimate a log-linear regression model where the response variable is the log rate ratio, the dose (rescaled to the referent dose) is the predictor, and the estimation procedure takes into account the correlation among rate ratios estimated using the same referent group (bottom quartile). Based on data presented in Table 5.4 the cancer mortality rate decreased by 12% (RR=0.88, 95% CI = 0.81-0.96) for every 4 MET-hours/day increment of total PA. Unsurprisingly, the linear trend estimated with the `glst` command on summarized data is very close to the linear trend estimated on original data reported in the abstract of Paper II (RR=0.88, 95% CI = 0.82-0.94) (Orsini, *et al.* 2008). Figure 5.21 graphically shows the linear trend estimated on summarized data that can be compared with the linear trend estimated on original data (Figure 5.6).

Figure 5.21 Multivariable mortality rate ratios for cancer in all sites according to total physical activity, expressed by MET-hours/day, estimated from dose-response summarized data.



Sensitivity analysis for biases

Conventional statistical methods to estimate exposure-disease associations from observational studies are based on several assumptions, such as no measurement error and no selection bias (i.e., selection, participation, and retention of subjects are purely random). One more assumption is also implicitly made if the exposure-disease association is interpreted as causal effect: random exposure assignment within levels of controlled covariates (Greenland 2008). When such assumptions are not met, tests and estimates of the association between exposure and disease are likely to be biased and may fail to capture most of the uncertainty around the estimated parameter (Greenland 2005). There are many proposed methods to adjust uncertainty assessments for unmeasured sources of bias or systematic error (Chu, *et al.* 2006, Eddy 1992, Fox, *et al.* 2005, Greenland 2001, Greenland 2003, Greenland 2005, Greenland 2008, Hoffman and Hammonds 1994, Lash and Fink 2003, Phillips 2003, Steenland and Greenland 2004). Nonetheless, few published papers in epidemiologic journals use quantitative methods to investigate the role of potential bias in the observed findings (Jurek, *et al.* 2006).

To facilitate the use of both deterministic and probabilistic sensitivity analysis, we present a flexible and easy-to-use tool to assess the uncertainty of exposure-disease associations due to misclassification of the exposure, selection bias, and unmeasured confounding. The proposed tool is implemented as a one-line Stata command. Paper VII illustrates the use of the tool by analyzing a published medical study reporting a positive association between occupational resin exposure and lung-cancer deaths in a case-control study used in previous methodological publications (Fox, *et al.* 2005, Greenland 1996).

We now illustrate the `episens` Stata command to perform a sensitivity analysis for misclassification of the exposure for the association between total PA and LUTS in the COSM (Paper I). For simplicity, we categorize the exposure, total PA, in two categories: sedentary (lowest quartile, <38 MET-hours/day) and active (second or higher quartile, >38 MET-hours/day). The easiest way to represent the data and analyze the association between a binary exposure and a binary health outcome is a standard contingency table (Table 5.5).

Table 5.5 Summarized data about the association between total physical activity categorized (sedentary, active), expressed in MET-hours/day, and moderate to severe lower urinary tract symptoms in the Cohort of Swedish Men.

Total physical activity	Median dose	Odds Ratio	95% Confidence Limits		Cases	Non Cases
<38	36	1.00	1.00	1.00	2022	5649
>38	43	0.77	0.72	0.81	4883	17823

The odds of experiencing moderate to severe LUTS was 23% lower (OR=0.77) among active men as compared to sedentary men. Further adjustment for age, waist-to-hip ratio, diabetes, alcohol consumption, smoking status, and years of education did not substantially change this association. Nonetheless, total PA must be misclassified to some extent.

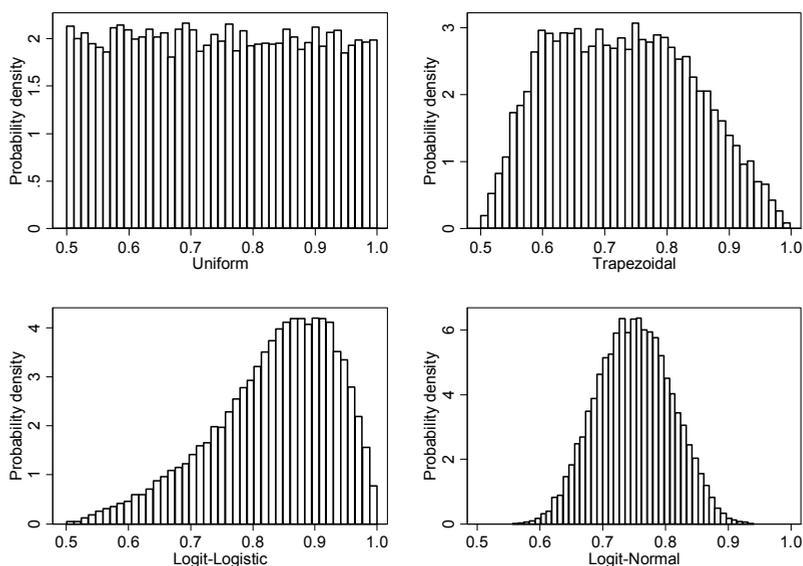
The basic idea of sensitivity analysis is to back calculate the data and exposure-disease association under hypothetical values for classification probabilities, called bias parameters, which reflects the severity of misclassification. Suppose no information is available about the sensitivity (probability that someone exposed is classified as exposed) and specificity (probability that someone unexposed is classified as unexposed) of the PA assessment. Regardless of the reference method used to evaluate the goodness of the questionnaire we can distinguish two extreme situations. In the worst scenario the sensitivity and specificity would be equal to 0.5, that is, there is a 50% chance of being correctly classified. In such case, the exposure classification of men based on the questionnaire is purely a random process (like flipping a coin, exposed if head and unexposed if tail). On the other hand, in a far too optimistic scenario the sensitivity and specificity would be equal to 1, that is, 100% of the men are correctly classified (no classification errors).

It is reasonable to assume that the true values of sensitivity and specificity will be somewhere between 0.5 and 1. Given the uncertainty around these bias parameters, we will assume a reasonable distribution of values. For instance, any value between 0.5 and 1 is possible but the interval of most likely and equally probable values may be between 0.6 and 0.8 (trapezoidal distribution). To obtain a distribution of bias-adjusted odds ratios we use a probabilistic or Monte-Carlo sensitivity analysis where we initially assume that classification errors (sensitivity and specificity) of total PA are not varying according to LUTS (non-differential misclassification of the exposure). Based on the above assumptions about the bias parameters and the possible mechanism of classification error, the median (of 10,000 possible scenarios) bias-adjusted odds of experiencing moderate to severe LUTS was 49% lower (OR=0.51) among active men as compared to sedentary men. Non-differential misclassification of PA yields attenuated estimate of the association between PA and LUTS. The percent bias, or relative difference, comparing the apparent (OR=0.77) and bias-adjusted (OR=0.51) odds ratios is about 51% $[(0.77-0.51)/0.51]$.

One could argue that in a cross-sectional study where both exposures (PA) and outcome (LUTS) are simultaneously reported, the mechanism underlying the classification of the exposure (sedentary, active) may operate differently according to the disease status (mild, moderate-to-severe LUTS). In other words, bias parameters may not be necessarily the same when comparing cases and non-cases (differential misclassification of the exposure). The **episens** Stata command allows one to introduce differential misclassification of the exposure by controlling the degree of correlation between bias parameters among cases and non-cases. A correlation equal to 1 indicates perfect non-differential misclassification and a correlation equal to 0 indicates perfect differential misclassification. For instance, assuming that the bias parameters among cases and non-cases are completely independent (correlation equal to zero), the median (of 10,000 scenarios) bias-adjusted odds of experiencing moderate to severe LUTS was 32% lower (OR=0.68) among active men as compared to sedentary men. Under differential misclassification the bias-adjusted OR became unpredictable (it could be far away from the null value) therefore there is much more uncertainty around it. However, based on the assumptions made about the bias parameters and differential misclassification, we could conclude that the observed or apparent odds ratio is likely to be lower than what it should be in the absence of bias, with a relative difference of about 13% $[(0.77-0.68)/0.68]$.

A validation study can provide useful insights about likely values for the bias parameters; therefore it could help the investigator to specify more accurate and realistic distributions for the classification probabilities in the adjustment of the apparent exposure-disease association. The **episens** Stata command allows the user to specify a variety of probability densities (i.e. uniform, trapezoidal, logit-logistic, logit-normal) for the bias parameters (Figure 5.22), and use these densities to obtain simulation limits for the bias adjusted exposure-disease measure of association.

Figure 5.22 Examples of probability distributions for bias parameters with range 0.5 to 1 that can be used in probabilistic sensitivity analysis.



6 DISCUSSION

6.1 MAIN FINDINGS

In this large population-based study of middle-aged and elderly men we observed an inverse association between current as well as past total PA and risk of LUTS (Paper I). Independently of the intensity of work/occupation, we observed a lower risk of moderate or severe LUTS for lower number of hours of inactive leisure-time, such as watching TV/reading. High long-term inactivity (5 hours per day or more) both at age 30 years and current, was associated with a 2-fold increased risk of LUTS. Longer time spent on leisure-time exercise (≥ 4 hours/week) and walking/bicycling (> 40 - 60 min/day) in early adulthood was associated with lower risk of urinary tract symptoms later in life, independently of current PA.

We observed a statistically significant strong inverse dose-response association between a quantitative score of total daily PA and cancer mortality (Paper II). Total daily PA corresponding to 1 hour of moderate effort was associated with 12% decreased mortality from cancer of all types. Overall, men in the top quartile of total of PA experienced consistently higher survival compared to those men in the lowest quartile throughout the time since diagnosis of cancer. The 5-year survival after cancer diagnosis was 77% for men who engaged in high levels of total PA and 69% for low activity levels. The main component of active living, walking or bicycling 30 minutes per day, was associated with a statistically significant 34% lower rate of death as compared to engaging in these activities on rare occasions. Furthermore, survival after cancer diagnosis was improved by 33% among those men who walk or biked 30 minutes per day. Association of total PA with cancer incidence was weak. However, walking or bicycling at least 60 minutes per day was associated with statistically significant 16% reduction in cancer incidence.

Obesity and physical inactivity were significantly associated with overall mortality (Paper III). In the highest PA level, overweight and obese men had a 60 percent higher death rate from all causes than lean men. Lean men with a low PA level had an increased rate of death from all causes (2-fold), cardiovascular disease (non-significant 60 percent), and cancer (2.5-fold). The excess mortality associated with obesity was not compensated for by a high level of PA.

A significant inverse linear dose-response association was observed between adult lifetime average duration of daily walking/bicycling and incidence of total, localized, and advanced prostate cancer in the range 30 to 120 minutes per day (Paper IV). Compared with men who walked or biked an average 30 min/day, every increment of 30 min/day was associated with a reduction of 8% for total, 9% for localized, and 12% for advanced prostate cancer incidence. No statistically significant changes in incidence rates of prostate cancer were observed below the lifetime walking/bicycling average duration of 30 min/day. Fatal prostate cancer rate was two-fold among men who hardly ever walked or biked compared with those men who maintained the highest lifetime average of 120 min/day, although this increase was not statistically significant.

Findings from our meta-analysis indicated that walking confers protection against coronary heart disease in a linear dose-response manner (Paper V). Every increment of 8 MET-hours per week, approximately equivalent to 30 min/day of moderate-intensity walking on 5 days per week, was associated with a statistically significant 19% reduced risk of CHD.

6.2 METHODOLOGY

Different sources of systematic errors or biases are likely to occur in observational studies: information bias; selection bias; and confounding. It is important to evaluate the role of bias as an alternative explanation for the observed associations in interpreting study results (Paper I-IV). The quantitative review of published observational studies is based on a weighted average of study-specific relative risks (Paper V). Therefore the result of a meta-analysis may be influenced by how much likely are the papers to be published (publication bias), degree of heterogeneity, and study-specific systematic errors.

Ideally, to quantify the magnitude and direction of bias the investigator should be able to specify and estimate a bias model for a certain exposure-disease measure of association. However, discussion of how sensitive are the observed findings to potential systematic errors requires knowledge of what are the parameters that govern the bias and what kind of data is available to support and fit the bias model. Therefore addressing quantitatively concerns about single or multiple biases is not easy. It follows a qualitative discussion of biases which is nonetheless important when results are likely to be used for public policy or medical practice recommendations.

Information bias

Information bias can occur whenever there are errors in the measurement of variables. For discrete variables, measurement error is usually called classification error or misclassification. For instance, our short PA questionnaire asked participants to remember duration (past year and distant past) of home/household work, walking/cycling, TV/reading, exercise and the intensity of work/occupation. A limitation of self-reported PA (current or historical) is that participants do not necessarily recall their activities accurately; they may tend to overestimate or underestimate duration and/or intensity of the activities. Furthermore, when we calculated a total PA score we assumed that all men performed the same type of activities, on average, at the same absolute intensity level and for work/occupation we assumed, on average, the same duration. Therefore the PA variables are likely to be affected by a certain degree of classification errors. The consequences of classification errors on the observed findings can vary, depending on whether or not the classification errors in the PA variables are related to the health outcome of interest. The parameters that control the bias due to misclassification of PA are the sensitivity and specificity of the method used to assess PA.

Differential misclassification of PA describes a scenario where the sensitivity and specificity varies according to the health outcome status (case vs. non-case). This is also known as recall bias where participants who developed the disease (cases) are asked to remember their prior habitual PA level. In case-control studies the sensitivity and specificity among cases and controls are likely to be different. It is reasonable to assume that men diagnosed with cancer may remember past PA (correctly or falsely) in a different way compared to controls. Under different values of sensitivity and specificity values among cases and non-cases the impact of classification errors on the observed exposure-disease association can be profound but it is difficult to predict the direction of the bias; the bias-adjusted exposure-disease association could be lower or higher than what it should be in the absence of bias.

Non-differential misclassification of PA describes a scenario where the sensitivity and specificity of the exposure do not vary according to the health outcome status. In prospective studies the exposure is assessed before the disease therefore differential misclassification is unlikely. Non-differential misclassification of the

exposure leads to dilution of the exposure-disease association. However, it has been shown that bias toward the null value may not be true if the exposure or disease has more than two levels or if the classification errors depend on errors made in other variables. For instance, in Paper III we analyzed the combined effect of obesity (as measured by BMI) and PA in predicting mortality, and both exposures were self-reported. If misclassification of PA is dependent on misclassification of body mass index the direction of the bias on the observed findings became unpredictable. However, it has been shown that self-report weight and height have higher reliability (Linear regression coefficient was 0.9 for both variables) compared with the actual measurement among Swedish men (Kuskowska-Wolk, *et al.* 1989), and there is no reason to expect correlated errors.

So far we discussed misclassification of the PA variable, the main exposure of interest in all our analysis, however, similar considerations apply to disease misclassification. In the analysis of the association between PA and LUTS both exposure and disease were self-reported (Paper I). Therefore we cannot exclude the possibility of misclassification of both PA and LUTS, which is likely to be non-differential leading to attenuation of the apparent association.

The Nordic countries have a long tradition of collecting data on deaths and diseases (Rosen 2002). They employ epidemiological registers (National Cancer Register, Hospital Discharge Register and the Causes of Death Register) of high quality covering the whole to inform the general public of the population. Causes of death have been registered in Sweden since 1751 (computerized from 1952). Using a unique personal identification number it is possible to link data on exposure or outcomes in these health data registers. In the analysis of the COSM we identified incident cases and deaths by linkage with these national and regional registries, both of which provide nearly 100% complete case ascertainment in Sweden (Paper II-IV). Therefore any potential bias due erroneous disease classification would have been minimal. Of note, it has been shown that if the number of false positives is negligible (probability someone non-diseased is classified as diseased) then imperfect non-differential sensitivity (probability someone diseased is classified as diseased) will not bias the relative risk (Greenland 2008).

Selection bias

Selection biases are distortions in the exposure-disease association that result from procedures used to select participants and from factors associated with study participation. This type of systematic error arises when the exposure-disease association is different for those who participated and all those who should have been eligible for the study, including those who did not participate into the study. The parameters that control the magnitude and direction of bias are the selection probabilities of the cases and non-cases in exposed and unexposed participants. The greater is the difference in the selection probabilities of cases and non-cases with respect to the exposure status and the greater is the bias. If determinants of participation are known, measured accurately and not affected by exposure and disease it is possible to estimate a bias-adjusted exposure-disease association using standard methods to deal with confounding factors.

A common source of selection bias is self-selection. A typical example is the “healthy-worker effect”; healthy people may be more likely to participate into the study and classified as physically active and less likely to have the disease. As such, the

healthy-worker effect is a form of unmeasured or uncontrolled confounding rather than selection bias. In prospective cohort studies exposed and unexposed participants are free from the disease of interest. Even assuming participants are less likely to have the disease, only a small association between participation and being physical active is expected. In other words, confounding by participation into the study is unlikely to have a strong impact on the observed PA-health outcome association.

Furthermore, if we assume that those men who did not answer the questionnaire are similar to those men who filled the questionnaire but only partially (i.e., missing PA values), then imputation of missing data may be viewed as an adjustment for non-participants' characteristics. If our observed findings were affected by "healthy-worker effect", then we would expect strong differences of the results when comparing observed and imputed data. In our analysis of the COSM we evaluated how sensitive were the observed findings to missing data using advanced statistical methods for multiple imputations (Paper I-IV). Overall, results based on complete subjects and multiply imputed datasets were very similar, indicating that the subsample of men included in the analysis was a random subset of the entire study population.

Unfortunately, not all selection bias in cohort studies can be treated as a form of confounding. For example, if being physically inactive causes loss to follow-up and to an increased risk of the disease then it is not possible to control for the bias as a confounder. The virtually complete follow-up of participants in the COSM through linkages to various population-based registries minimized the possibility that our findings based on the cohort were biased by differential follow-up.

Confounding

Confounding occurs when the observed exposure-disease association (or lack of one) is distorted because of extraneous factors mixed with the actual exposure effect (which may be null). The parameters that govern the magnitude and direction of bias are the confounder-exposure and the confounder-disease associations. Confounding can lead to overestimation, underestimation, or even change in the direction of the apparent exposure-disease association. Moreover, bias would not be fully controlled if the confounders were measured with errors, in such cases residual confounding continues to persist.

In our analysis of PA in relation to different health benefits (Paper I-IV) we controlled for many factors (anthropometric, socio-demographic, lifestyle) and age-adjusted and multivariable adjusted associations were overall similar. The most important predictor of the health outcomes investigated was age, which was measured with no error from the Swedish personal identification number.

Publication bias

One of the main concerns in quantitative review of epidemiological studies (Paper V) is that statistically significant results are more likely to be published as compared to non-significant results. In our dose-response meta-analysis we found no evidence of publication bias using both graphical (Funnel plot) and statistical methods (Egger's regression asymmetry test). However, rejecting the hypothesis of publication bias does not imply that our meta-analysis is completely extraneous to this type of bias.

Unpublished null findings would attenuate the observed dose-response trend between walking and CHD risk.

Generalizability

We showed that participants from the population-based COSM represents well the overall population of men in Sweden, since the distribution of age, relative weight, and educational level was almost identical to the entire Swedish population of middle-aged and older men. Given the internal validity without evidences of strong biases as discussed above, the external validity should also be satisfactory and our findings should be most directly generalizable to middle-aged and elderly Swedish men.

Moreover, our results are probably generalizable to most high-income and urban-industrial settings in all continents and most countries throughout the world, since increasing sedentary ways of life is not only a Swedish phenomenon.

6.3 INTERPRETATIONS

All our results are confirming to the body evidence that maintaining moderate PA, which can be accumulated in many different ways (occupational, household, transport, and recreational), is associated with several health benefits. Our findings are consistent with the message that the more physically active people are the more health benefits they gain.

Physical activity and lower urinary tract symptoms

A recent quantitative review of PA and LUTS and BPH based on eight cross-sectional studies concluded that PA reduces the risks of BPH and LUTS (Parsons and Kashefi 2008). Compared to the sedentary group, the combined odds ratios for BPH or LUTS were 0.70 (95% CI=0.44-1.13), 0.74 (95% CI=0.60-0.92), and 0.74 (95% CI=0.59-0.92) for men engaging in light, moderate, and heavy PA, respectively.

Our findings in Paper I about total PA (most active vs. least active OR=0.72; 95% CI = 0.66-0.79) are therefore consistent with previous studies. Furthermore, our result of an inverse association between distant young adulthood total PA and risk of LUTS later in life is in agreement with a study reporting pathologic signs of BPH already at ages 31-40 years and concluding that the initiation of BPH growth is likely to start before age 30 years (Berry, *et al.* 1984).

Physical activity and all site cancer incidence and mortality

Several epidemiological studies investigated the association between PA of all types and the risk of developing various types of cancer. Evidence suggests that higher rather than lower levels of PA protect (colon, breast), or may protect (endometrium, lung, pancreas, prostate) a numbers of cancers (PAGAC 2008, WCRF/AICR 2007).

In Paper II we analyzed cancers from all causes, and we found a non-significant inverse association between walking or bicycling for 30 minutes per day and cancer incidence. A longer duration, however, of daily walking or bicycling for at least 60 minutes was significantly associated with 16% lower risk of cancer. This finding supports the PA recommendation of the World Cancer Research Fund / American Institute for Cancer Research which calls, as fitness improve, for moderate activity of

longer duration, namely 60 minutes per day or more, which can be incorporated in occupational, household, or leisure-activities (WCRF/AICR 2007).

The finding that cancer mortality decreased linearly with total PA is in agreement with a previous large prospective study among 252,925 participants 50 to 71 years which observed a significant (P for trend= 0.02) inverse relationship between cancer mortality and the number of hours per week of activity of at least moderate intensity (Leitzmann et al, 2007). Similar to our study, the authors did not observe any effect modification by smoking, age or BMI. The finding that men in the top quartile of total PA had 29% lower rate of all-cancer death is in agreement with a previous prospective cohort (Hu et al, 2005). In this study, after 17.7 years of follow-up (2039 cancer deaths) a significant protective effect (20%) of combined leisure-time and occupational PA was observed on all cancer related mortality comparing the highest versus the lowest category of PA (Hu et al, 2005). This previous study, however, assessed PA only in a qualitative manner (low, medium, high) whereas in our data we modeled total daily PA as a continuous quantitative score and we found an inverse linear dose-response trend without a plateau. The clinical significance of this observation is that there is no threshold above which the beneficial effect of PA ceases to exist.

Obesity, physical activity and mortality

Two leading causes of mortality, both in Sweden as well as globally, are cardiovascular disease and cancer. The evidence is strongly persuasive that PA reduces the occurrence of these two leading cause of death (PAGAC 2008, WCRF/AICR 2007). Paper III investigated the combined association of two important predictors, PA and obesity, in predicting all-cause, cardiovascular, and cancer mortality (Blair and Brodny 1999).

Although some prospective studies investigated the joint effects of obesity and PA on mortality risk among men, (Hu, *et al.* 2005, Lee and Paffenbarger 2000, Vatten, *et al.* 2006) none of the previous studies use strict exclusion criteria to attenuate the problem of reverse causation (Willett, *et al.* 2005).

A study among 13,485 men from the Harvard Alumni Health Study where 2538 deaths occurred during 15 years of follow-up reported that lean inactive men (based on leisure-time and sport/recreational activity) had a 50 percent higher (2-fold increase in our study) death rate from all-causes compared to lean active men (Lee and Paffenbarger 2000). A Norwegian study among 32,872 men followed for 16 years with 3526 deaths from cardiovascular disease found a 2-fold increase death rate for obese and never active men compared with normal weight and highly active men (Vatten, *et al.* 2006). However, no evidence (RR=1.06) of increased cardiovascular death rate was found among normal weight and inactive men compared with normal weight but highly active men (Vatten, *et al.* 2006). A Finnish study of 22,528 men with almost 18 years of follow-up and 4563 total deaths investigated the joint effects of BMI and PA (combination of leisure-time and occupational) on total mortality as well as cardiovascular and cancer mortality (Hu, *et al.* 2005). Among inactive and obese men, compared with the active and normal weight men, the mortality rate ratio for total mortality was 1.78 (2.04 in our study), for cancer was 1.32 (2.02 in our study), and for cardiovascular disease was 2.09 (1.72 in our study).

It has been shown that physical fitness, as measured by the treadmill-exercise test, is a stronger predictor of all-cause mortality compared to PA measured by a questionnaire (Myers, *et al.* 2004). A study of 21,925 men where 428 deaths occurred during 8 years of follow-up reported that obese men who were fit did not have elevated all-cause and cardiovascular mortality as compared to lean men (Lee, *et al.* 1999). The

Lipid Research Clinics Study among 2603 adults aged 60 years or older, however, concluded that both fitness and fatness were risk factors for mortality, and that being fit does not completely reverse the elevated mortality associated with excess adiposity (Sui, *et al.* 2007). Even though we did not assess physical fitness, given that PA is closely related to physical fitness, our findings are in agreement with the conclusion of the Lipid Research Clinics Study.

Physical activity and prostate cancer

A large number of studies have investigated the association between PA and prostate cancer risk, and in summary, due to inconsistent findings, a recent report noted that PA may reduce risk specifically of advanced or aggressive cancer of the prostate, but no formal judgment was made regarding the strength of the evidence (WCRF/AICR 2007).

Our finding that the highest level of lifetime walking/bicycling, averaged over about 40 years prior to diagnosis, was associated with 17% reduced risk of total prostate cancer is consistent with a previous Canadian case-control study which reported a non-significant 20% reduced risk of all prostate cancer for the top lifetime recreational level (Friedenreich, *et al.* 2004). Our finding about the inverse association between lifetime walking or bicycling for 1 hour per day or more and prostate cancer incidence supports the PA recommendation of the World Cancer Research Fund/American Institute for Cancer Research which calls for moderate activity of longer duration, namely 60 minutes per day or more (WCRF/AICR 2007). Furthermore, our finding on the strong inverse association (27% risk reduction) between lifetime walking or bicycling for more than 1 hour per day and advanced prostate cancer is supporting a previous large prospective cohort study of American men (Patel, *et al.* 2005). In the American Cancer Society Cancer Prevention Study II Nutrition Cohort baseline recreational PA (recent past only) corresponding to 35 MET-hours per week or more (roughly corresponding to 1 hour of walking/bicycling per day or more) was associated with a statistically significant 31% risk reduction for aggressive prostate cancer (Patel, *et al.* 2005).

In the Health Professional follow-up study, a strong inverse association (around 70% risk reduction) between recent past vigorous PA and metastatic prostate cancer was observed only in men 65 years or older, with evidence of effect modification by age (Giovannucci, *et al.* 2005). In our analysis we found no evidence of heterogeneity in the relationship between lifetime walking/bicycling and prostate cancer risk across subgroups defined by age as well as waist-to-hip ratio.

Physical activity and coronary heart disease

The evidence for a protective effect of moderate PA against CHD morbidity and mortality is strong (PAGAC 2008, Pate, *et al.* 1995, USDHHS 1996). A recent extensive review of more than 60 studies in men and women of the association between habitual PA and CHD risk found a median risk reduction of 20% for moderately intensive activity versus none or light activity. More active men experienced a lower fatal or non-fatal CHD with no difference in CHD incidence versus mortality (PAGAC 2008). The 19% CHD risk reduction associated with moderate-intensity walking approximately 30 min/day on most days of the week estimated in the dose-response meta-analysis (Paper V) is therefore consistent with previous reviews of PA and CHD risk (Kohl 2001, PAGAC 2008, USDHHS 1996).

6.4 BIOLOGICAL MECHANISM

PA has marked effects on many functions of the human body. Therefore multiple pathways to explain the link between PA and a healthy body are plausible.

LUTS of increasing severity with increasing age are often manifestations of BPH. The etiology and natural history of LUTS and BPH are not well understood. Previous causal models have focused primarily on sex hormones, which are essential to normal prostate growth and development, and genetic predisposition. However, several large studies showed that increased levels of a modifiable factor like PA have been associated with a decreased risk of BPH and LUTS, suggesting therefore the need to find other possible explanations (Parsons 2007). The accumulating evidence supports the role of overactivity of the autonomic nervous system and hyperinsulinaemia for development and progression of LUTS (McVary, *et al.* 2005). Increasing PA to moderate levels over the long terms reduces sympathetic nervous system activity at rest in general (Platz, *et al.* 1998). Thus it would be biologically plausible that physically active men have less LUTS what might be in part mediated by reduction in sympathetic nervous tone. An increased insulin concentration (hyperinsulinemia/insulin resistance) is also associated with increased sympathetic nervous system activity (Rohrmann, *et al.* 2004). Furthermore, a recent review of the association between PA and LUTS/BPH indicated that PA's beneficial effects lie largely in its role in improving cardiovascular health (Parsons and Kashefi 2008).

PA has been associated with risk of various forms of cancers, and several plausible mechanisms have been proposed to explain the links between PA and cancer risk and prognosis (McTiernan 2008, PAGAC 2008, WCRF/AICR 2007). Increased PA reduces the amount of adipose tissue, which may explain reductions in cancers that are associated with overweight and obesity (colon, pancreas, breast, endometrial). Increased PA is associated with reduced levels of sex hormones, which may explain a link between PA and hormone-related cancers (breast, endometrial, prostate). Another possible mechanism is through the effect of PA in reducing inflammatory markers and increasing adiponectin levels (most cancer types). Moreover, increased PA reduces insulin resistance and glucose, which could explain associations with risk for some cancers that may be increased in individuals with insulin resistance or hyperinsulinaemia (colon, pancreas, breast, endometrial). The relationship between PA and immune function has not been well studied, PA could improve the number or function of natural killer cells, which have a role in tumor suppression (McTiernan 2008).

The biological mechanisms that explain why regular PA decreases CHD risk are not fully known but include factors mainly related to myocardial oxygen supply and demand and myocardial electrical stability. The major CHD risk factors (e.g. hypertension, hyperlipidemia, obesity, and diabetes) are modifiable by PA changes. The mechanisms best supported by scientific evidence are increased HDL cholesterol, decreased body weight and blood pressure, and improved glucose tolerance (PAGAC 2008).

The totality of the evidence about the strong and inverse association between PA and lower mortality rates from all causes may be explained by the plausible mechanisms that exist between PA and decreased occurrence of CVD and cancer, the leading causes of mortality worldwide (PAGAC 2008).

7 FUTURE RESEARCH

The fact that PA is associated with health has been known for a long time and a substantial amount of scientific literature has been published on the epidemiology of PA during the last decades. However, many areas still need to be further explored: understudied subpopulations (i.e. individuals with specific disabilities); shape of the dose-response curve (i.e. focus at the tails of the PA distribution); understudied health outcomes (i.e. specific forms of cancer); and assessment of PA (i.e. evaluation of new technologies to be used in large free-living populations).

There are some methodological considerations needed to be taken into account in future studies when exploring the role of PA and health benefits. The epidemiology of PA would greatly benefit from more homogenous and reliable data collection, data analysis, and data presentations of either observational or experimental studies.

It is important to use validated instruments, since high validity and precision are indispensable to detect an association, especially when this is weak. Furthermore, validation data can provide useful information to perform a sensitivity analysis of the observed findings to potential systematic errors in order to capture the overall uncertainty around them. More reliable data would not only decrease the differences in results across studies, but it could also facilitate dose-response quantitative reviews of the increasing number of published papers in the field.

8 CONCLUSIONS

On the basis of our findings we conclude that:

- Higher levels of physical activity during young and late adulthood are associated with a lower risk of moderate and severe lower urinary tract symptoms.
- Higher levels of physical activity and the main component of active living, walking or bicycling, are associated with reduced cancer incidence and mortality as well as enhanced survival after cancer diagnosis.
- Both overweight and physical inactivity are important predictors of mortality. Higher level of physical activity does not compensate the excess mortality associated with overweight.
- Walking or bicycling more than 30 minutes per day during adult life may be associated with reduced incidence of prostate cancer.
- Every increment of 30 minutes per day of moderate-intensity walking on most days of the week decreases coronary heart disease risk by about 20% in a linear dose-response manner.

Based on the statistical components developed for Stata® software and explained by the methodological papers we conclude that:

- The **glst** command greatly facilitates trend estimation of single or multiple studies in dose-response meta-analysis.
- The **episens** command greatly eases the quantitative discussion of how sensitive the observed findings are to possible systematic errors such as exposure misclassification, selection bias, and uncontrolled confounding.

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10 SAMMANFATTNING (SUMMARY IN SWEDISH)

På grund av sin betydelse för hälsa och sjukdomsprevention är fysisk aktivitet ett speciellt viktigt hälsobeteende att undersöka. Syftet med den här avhandlingen var att: mäta sambanden mellan fysisk aktivitet och olika sjukdomstillstånd (nedre urinvägssymtom, canceruppkomst, och dödlighet) i Kohorten av Svenska Män (COSM); att göra en dos-respons metaanalys över publicerade samband mellan gång och uppkomst av hjärtsjukdom; och att tillhandahålla ett användarvänligt mjukvarupaket för att göra dos-respons metaanalyser och sensitivitetsanalyser över felkällor i observationella studier.

COSM är en populationsbaserad prospektiv kohort som inkluderar 45,906 män mellan 45 och 79 år från centrala Sverige som var utan cancer och fyllde i ett frågeformulär om nuvarande och tidigare fysisk aktivitet, kost, och andra livsstilsfaktorer vid starten 1997.

Vid starten rapporterade 6905 män måttliga till allvarliga nedre urinvägssymtom (LUTS). Total fysisk aktivitet var signifikant omvänt kopplat till måttligt till allvarligt LUTS (högsta mot lägsta kvartilen av odds ratio=0.72; 95% konfidensintervall (CI)=0.66-0.79). Män som var fysiskt aktiva både på arbetet och på fritiden hade en halverad risk för måttligt till allvarligt LUTS (95% CI=0.40-0.60) jämfört med inaktiva. Lång tid av hög inaktivitet (5 timmar per dag både vid 30 års ålder och vid studiens start) var associerat med en dubblerad risk (95% CI=1.41-2.59) jämfört med dem som var mer aktiva vid båda tillfällena.

Under 7 års uppföljning blev 3714 män diagnostiserade med cancer och 1153 dog av cancer. Vi observerade ett starkt omvänt linjärt samband mellan total daglig fysisk aktivitet och dödlighet i all cancer. För varje ökning av 4 metaboliska ekvivalenter (MET)-timmar/dag av total fysisk aktivitet (ungefär 1 timmes daglig måttlig ansträngning) minskade cancer uppkomsten med 2% och dödligheten av cancer minskade signifikant med 12 % (95% CI=6-18%).

Under 9.7 år av uppföljning identifierade vi totalt 4086 dödsfall. Jämfört med män som var smala (body mass index (BMI) <25kg/m²) och aktiva (högsta tertilen av total fysisk aktivitet) var den justerade rate ration för död av alla orsaker 1.44 (95% CI=1.11-1.86) för feta (BMI≥30kg/m²) och aktiva män, 1.54 (95% CI=1.34-1.77) för smala (BMI<25) men inaktiva (lägsta tertilen) män, och 1.81 (95% CI=1.48-2.23) för feta inaktiva män. Efter att ha exkluderat de första 3 åren av uppföljningen, rökare och före detta rökare, de som hade gått ner i vikt från 20 års ålder fram till studiestarten, och de med tungt kroppsarbete, blev den justerade rate ration för död av alla orsaker 1.65 (95% CI=1.20-2.27) för överviktiga eller feta aktiva män, 2.15 (95% CI=1.59-2.91) för smala inaktiva män, och 2.04 (95% CI=1.52-2.74) för överviktiga eller feta inaktiva män jämfört med smala aktiva män.

Under 10 års uppföljning blev 2735 män diagnostiserade med prostatacancer, av dem avled 190 män. Vi observerade ett omvänt linjärt samband mellan livstids (genomsnitt vid år 30, 50 och studiestart) gång/cykling och uppkomst av prostatacancer. Den justerade rate ration minskade med 8% (95% CI=2-13%) för varje 30 min/dag ökning av livstids gång/cykling inom omfånget 30 till 120 min/dag. Den dödliga prostatacancerrisken bland de män som nästan aldrig gick eller cyklade var

dubbelt så hög som den bland män i den högsta gruppen av genomsnittlig livstids gång/cykling med 120 min/dag, denna ökade risk var dock inte signifikant.

I dos-respons metaanalysen av epidemiologiska studier fann vi att varje ökning av 8 MET-timmar/vecka (ungefär 30 minuter av gång varje dag) var associerad med 19% minskad risk för hjärtsjukdom (95% CI=14-23%).

Sammantaget visar våra resultat på att ökad fysisk aktivitet kan minska risken för nedre urinvägssymtom, dödlighet av alla orsaker och av cancer, prostatacancer, och hjärtsjukdom.

Dessutom kan de två statistikkomponenterna utvecklade för programvaran Stata® underlätta dosrespons metaanalys (**gls**) och stödjande sensitivitetanalyser (**episens**) av epidemiologiska resultat.

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