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physical activity in men and relation to prostate cancer

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SUMMARY

Physical activity is hypothesized to reduce the risk of several chronic diseases and enhance longevity. Low levels of activity have been associated with some but not all types of cancers. Although an association with physical activity and prostate cancer – the most common cancer among Swedish men and with an increasing incidence – is biologically plausible, results from published studies are inconclusive. Most of the questionnaires used measure only part of total physical activity – leisure-time activity and/or occupational – which might lead to misclassification of total physical activity level and to dilution of risk estimates. Moreover, despite a large public health interest in physical activity, and the fact that the incidence of many chronic diseases associated with physical inactivity, is increasing over time and with age, only few reports to date have addressed levels and trends of different types of physical activity by age and over time.

We evaluated the validity and reproducibility of a short self-administered physical activity questionnaire, intended to measure present *total* daily 24-hour physical activity (*Paper I*). The questionnaire included questions on level of physical activity at work, hours per day of walking/bicycling, home/household work, leisure-time activity/inactivity, and sleeping. Levels of total activity were quantitatively assessed by adding the activities together and measured as MET-hours/day (metabolic equivalents of resting metabolic rate). One hundred eleven men in central Sweden, aged 44-78, completed the questionnaire and one or two 7-day activity records used as the reference method. Spearman correlation coefficient was 0.56 between total daily activity score estimated from the first questionnaire and activity records (validity) (r=0.69 when deattenuated for random error in the questionnaire) and 0.65 between the first and a second repeated questionnaire (reproducibility). Significantly higher validity correlations were observed in men with self-reported body mass index below 26 kg/m^2 than in heavier men. We conclude that our questionnaire may be considered a valid instrument for assessing total physical activity.

Levels of *total* physical activity and different types of activities were studied in relation to (1) age in a cross-sectional setting (*Paper II*), (2) age in a longitudinal setting and (3) calendar-time (*Paper III*). In a population-based cohort of 33,466 men aged 45-79 years in central Sweden, we collected information on levels of total current physical activity (the validated self-administered questionnaire), and retrospectively at ages 15, 30 and 50 years. Total daily physical activity decreased with age, both in cross-sectional (-4% from age 45 to 79) and in longitudinal analyses (-4% from age 15 to 50). The decrease was greatest among obese men, current smokers, low-educated men, and men with low self-rated health in cross-sectional analyses. Total physical activity decreased over a period of 60 years in all age groups (15, 30, 50 years).

Effects of occupational physical activity on risk for prostate cancer were investigated in a nationwide cohort that was established through linkage between Swedish census data in 1960 and 1970, and the Cancer register 1971-1989 (*Paper IV*). Physical activity levels at work were classified based on the codes for occupational titles in the census. A total of 19,670 prostate cancers occurred during the 19 years of follow-up in the cohort of men with the same physical activity level in 1960 and 1970 (n=673,443). Sedentary men had a small but statistically significant increased risk of 11% as compared to men with a very high/high activity level.

In conclusion, we observed a slightly increased risk for prostate cancer in men with sedentary and light occupations. From a public health point of view, observed decreasing levels of total physical activity both with age and over time (last 60 years), require undertaking of effective preventive strategies since many chronic diseases associated with physical inactivity have been increasing over time.

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LIST OF PUBLICATIONS

This thesis is based on the following papers, referenced to by their Roman numerals:

I *Norman Anna, Bellocco Rino, Bergström Anna, Wolk Alicja.*
Validity and reproducibility of self-reported total physical activity – differences by relative weight.
Int J Obes Relat Metab Disord. 2001; 25: 682-8.

II *Norman Anna, Bellocco Rino, Vaida Florin, Wolk Alicja.*
Total physical activity in relation to age, body mass, health and other factors in a cohort of Swedish men.
Int J Obes Relat Metab Disord. 2002; 26: 670-5.

III *Norman Anna, Bellocco Rino, Vaida Florin, Wolk Alicja.*
Age and temporal trends of total physical activity in Swedish men.
Med Sci Sports Exerc. 2003; 35: 617-22.

IV *Norman Anna, Moradi Tahereh, Gridley Gloria, Dosemeci Mustafa, Rydh Bosse, Nyrén Olof, Wolk Alicja.*
Occupational physical activity and risk for prostate cancer in a nationwide cohort study in Sweden.
Br J Cancer. 2002; 86: 70-5.

CONTENTS

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
COSM	cohort of Swedish men
IGF	insulin-like growth factor
LTPA	leisure-time physical activity
MET	metabolic equivalent of resting metabolic rate
NA	not applicable
OPA	occupational physical activity
PAL	physical activity level
PAQ	physical activity questionnaire
PSA	prostate specific antigen
RR	relative risk
SHBG	sex hormone binding globulin

INTRODUCTION

The human body is made for moving, and walking has been the primary means of land transportation until the last hundred years. Our body is now essentially maladjusted in our sedentary environment and the promotion of a physically active lifestyle is an important public health objective. Low levels of physical activity are associated with several chronic diseases and as a consequence, physical activity is associated with all-cause mortality (Paffenbarger et al. 1986; Hakim et al. 1998). There is a strong inverse association between physical activity and cardiovascular disease, stroke and hypertension (Bijnen et al. 1994; Wannamethee et al. 1998). Studies also show an association between lower levels of physical activity and obesity (Coakley et al. 1998; Martinez-Gonzalez et al. 1999), type II diabetes (Steyn et al. 2004), hip fracture (Cooper et al. 1988; Branca 1999; Manson et al. 2004) and certain types of cancer, especially colon cancer (Kiningham 1998; American Cancer Society 2002; Friedenreich et al. 2002; IARC 2002). Epidemiological studies on physical activity and prostate cancer risk have been inconclusive, but suggest a protective effect with higher levels of activity (Lee et al. 2001b; IARC 2002). Furthermore, high levels of physical activity maintain functional capacities such as muscular strength, endurance and mobility which improve measures of quality of life, especially among older persons and for a healthy aging (IARC 2002). Physical activity is also related to psychological health (U.S. Department of Health and Human Services 1996).

Physical activity is a complex behavior and is difficult to measure in large populations. Questionnaires used for estimating physical activity in large-scale epidemiological studies differ in focus, time period, and data collecting method (self-administered or interview) (Washburn et al. 1986; Montoye et al. 1996). Most questionnaires measure only a fraction of the physical activity, for example physical activity at work, sporting-frequency or leisure-time activities, while in fact the *total* physical activity might be of importance, especially for obesity, but also since biological mechanisms are not clearly understood for cardiovascular disease and cancer.

Despite a large public health interest in physical activity, and the fact that the incidence of many chronic diseases associated with physical inactivity is increasing with age and over time, only few reports to date have addressed levels of different types of physical activity over calendar-time (U.S. Department of Health and Human Services 1996). Most studies concentrate on leisure-time physical activity or exercise. Due to higher prevalence of sedentary jobs, labor saving devices in the home and the workplace, motorized transports and leisure-time video, computer and internet use, and since there is no need for physical activity for transportation, food-seeking, or daily survival, total physical activity has decreased over time which is reflected by increasing prevalence of obesity (Lissner et al. 2000; Manson et al. 2004). However, to our knowledge, changes in total physical activity levels over calendar-time or by age have not been quantified.

BACKGROUND

Assessment of physical activity

Physical activity has been defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (Caspersen et al. 1985). 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 physical activity (Ravussin et al. 1992). *Exercise* is a "specific type of physical activity that is planned, structured, and repetitive and done to improve or maintain physical fitness. *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 physical activity (Caspersen et al. 1985; Howley 2001). Moreover, it is important to differentiate between physical activity and *energy expenditure* (Lamonte et al. 2001). Physical activity is a behavior that results in energy expenditure. Energy expenditure reflects the energy cost or intensity associated with a given physical activity.

Several techniques have been used to estimate physical activity and energy expenditure in the field (LaPorte et al. 1985; Melanson et al. 1996). However, validity, reproducibility and objectivity of many of these methods are not clear. Moreover, validation of any of these methods is difficult because of the lack of a commonly accepted "gold standard" (Jacobs et al. 1993). *Validity* refers to the degree to which a measurement process really measures what is intended, i.e. whether the measurement systematically deviates from the true value or not. *Reproducibility* refers to the amount of random error in the measurements, i.e. the ability to yield the same result if it is applied on a second occasion under the same circumstances (Willett 1998). Frequency, duration and intensity are three important factors to consider when estimating physical activity (Howley 2001).

OBJECTIVE ASSESSMENT OF PHYSICAL ACTIVITY

There are different methods for measuring physical activity, and some of the methods used are presented below. The *doubly labeled water* is considered to be the most accurate method, measuring the disappearance rate of labeled water isotopes from urine samples to estimate carbon dioxide production (Schoeller et al. 1982). A limitation of this technique – besides 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. *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 physical activity (Melanson et al. 1996). Moreover, the linear relationship may not be accurate during low and very high intensity activity (Lamonte et al. 2001). The use of *accelerometers* or *motion detectors* to measure activity is based on the assumption that accelerations of the limbs and torso closely reflect energy cost but the specific type of physical activity is unknown (Lamonte et al. 2001).

SELF-REPORTED PHYSICAL ACTIVITY

Although somewhat limited in its objectivity, *self-reported physical activity* is more appropriate than the above mentioned methods and commonly used in large-scale epidemiological studies, since it is relatively easy to administer and relatively inexpensive (Melanson et al. 1996). The procedure does not influence the subjects' activities to the extent that can occur with observation, diary keeping or the above mentioned methods. Preferably, *frequency, duration* and *intensity* of the specific activity during a particular time frame are needed to estimate the physical activity performed (Kriska et al. 1997). Frequency is the number of activity sessions per day, week, or month, and duration refers to the number of minutes/hours of activity in each session. Intensity describes the effort associated with the physical activity.

Different types of questionnaires

However, physical activity questionnaires used vary in their complexity, from self-administered, single-item questions to interviewer-administered surveys of lifetime physical activity (Washburn et al. 1986; 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. the past week, month, year or even over a lifetime. Questionnaires focusing on a longer time frame, such as one year, are more likely to reflect usual activity patterns. Most of the questionnaires measure only a fraction of the physical activity, for example, activity at work, sporting frequency or leisure-time activities (Albanes et al. 1990; Melanson et al. 1996; Pereira et al. 1997) and the two principal categories of physical activity used are occupational physical activity and leisure-time activity. Occupational activity usually refers to an 8-hour day, whereas the duration of leisure-time physical activity 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 physical activity performed to improve or maintain physical fitness as described above (Howley 2001). Household activities also contribute to the daily physical activity and are important to include in the questionnaire. Scoring systems vary among questionnaires, ranging from simple ordinal scales (e.g. 1-5, low to high physical activity), to a summed score of continuous data (e.g. $kcal \cdot d^{-1}$) (Lamonte et al. 2001). For some activity questionnaires, an index of total activity is estimated (Friedenreich et al. 1998), based on the types of activities asked for and not adding up to 24 hours, and only a few questionnaires aim at estimating 24-hour total physical activity (Arroll et al. 1991; Pols et al. 1997).

Time considerations often require the use of brief surveys that measure the most common physical activities of a population. Estimating exercise only may however give a distorted understanding of the levels of total physical activity, since a heavy manual worker with no leisure-time activity would be classified as inactive, while a sedentary worker that engages in tennis once a week would be active. Moreover, since it is not always clear what pattern or type of physical activities are related to positive benefits, especially for cancer, consideration must be given to whether a specific type of activity such as exercise or occupation or the overall level of activity is of interest to obtain information about (Washburn et al. 1986).

Quantifying physical activity

A compendium of physical activities for coding specific activities by type and intensity was published by Ainsworth and coworkers and is widely used in epidemiological studies of physical activity (Ainsworth et al. 1993; Ainsworth et al. 2000). It was developed to enhance the comparability of results across studies using self-reports of physical activity. The compendium coding scheme links a five-digit code that describes physical activities by major headings (e.g., occupation, transportation) and specific activities within each major heading with its intensity, defined as the ratio of work metabolic rate to a standard resting metabolic rate (MET). One MET is also defined as sitting quietly, which for the average adult requires is approximately 3.5 ml of oxygen per kg of body weight and minute or 1 kcal per kg body weight and hour. Energy expenditure units for METs can be expressed in MET-minutes, MET-hours, kcal, or kcal per kilogram body weight for specific activities during a certain time period (Ainsworth et al. 1993). However, most standard compendia of metabolic costs are based on data for young adults, and they tend to overestimate the intensity of activity in middle aged and older people (Shephard 2003). A different way of quantifying physical activity levels is to express daily energy expenditure as multiples of basal metabolic rate (the minimum energy expenditure per day) in *PAL units* (Physical Activity Level) (World Health Organization 2000). Individuals whose occupation involves regular physical exercise are likely to have PAL values of 1.75 and more. Those whose lifestyle involves only light occupational and leisure-time activity have PAL values of approximately 1.55-1.60. People who engage in no activity whatsoever have PAL values around 1.4 (World Health Organization 2000).

Limitations

Limitations with self-reported physical activity may be that subjects do not necessarily recall their activities accurately; they may tend to overestimate time or intensity (Montoye et al. 1996). Detailed questionnaires and interview place a considerable burden on subjects. Moreover, even if frequency and time are recalled correctly, it may be difficult to estimate the intensity of activities.

Physical activity in the population

Recommendations for physical activity in the U.S. are that every adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week (Pate et al. 1995). Examples given for moderate-intensity activities are brisk walking, cycling for transportation or pleasure, swimming, conditioning exercise, playing golf, home care, general cleaning, fishing, mowing lawn (power mower), home repair and approximately 200 kilocalories per day should be expended in these types of activities (Pate et al. 1995). These recommendations have been adapted in many countries, as well as in Sweden (Statens folkhälsoinstitut 2003). Despite a large public health interest in physical activity, only few reports to date have addressed levels and trends of different types of physical activity over calendar-time, but this issue is becoming more high-lighted. Most reports focus on exercise and leisure-time activity (U.S. Department of Health and Human Services 1996). However, to our knowledge, there is no information on changes in *total* physical activity levels with age, different lifestyle factors and over calendar-time.

LEISURE-TIME ACTIVITY AND AGE

The prevalence of regular leisure-time physical activity/exercise has been shown to decrease with age in several studies worldwide, both in young adulthood and at older ages (Lee et al. 1992a; Engström et al. 1993; Anderssen et al. 1996; Barnekow-Bergkvist et al. 1996; Raitakari et al. 1996; Schmitz et al. 1997; Burton et al. 1999; Hays et al. 1999; Ruchlin et al. 1999; Booth et al. 2000; Salmon et al. 2000) and age is one of the most consistent correlates of physical activity behavior in adults (Trost et al. 2002). Adults at retirement age (65 years) show some increased participation in activities of light to moderate intensity, but overall, physical activity declines continuously as age increases (Pate et al. 1995; Booth et al. 2000).

LEISURE-TIME ACTIVITY AND LIFESTYLE FACTORS

Leisure-time physical activity has been shown to be associated with different demographic characteristics. Higher levels of physical activity have repeatedly been observed in *men* compared to women (Trost et al. 2002). People with higher *education* participate in more leisure-time physical activity than do people with lower education (Caspersen et al. 1986; Engström et al. 1993; Salmon et al. 2000; Craig et al. 2004). Similarly, *socio-economic status* is positively associated with physical activity (Salmon et al. 2000; Trost et al. 2002). *Cigarette smoking* has been shown to be only weakly inversely associated with participation in exercise, but smokers are more likely than nonsmokers to drop out of exercise programs (Pate et al. 1995; Salmon et al. 2000). *Marital status* has been related to exercise level, where married men seem to have lower levels of activity (Salmon et al. 2000). *Obesity* and high body weight have been associated with a sedentary lifestyle and lack of physical activity (Martinez-Gonzalez et al. 1999; Trost et al. 2002). Perceived *health* has also been reported to be associated with physical activity. A low health status correlates with a low level of activity (Burton et al. 1999; Ruchlin et al. 1999; Trost et al. 2002). Other factors that have been correlated to physical activity patterns and recently have been reviewed are some psychological, cognitive and emotional factors (e.g. enjoyment, expected benefits, self-motivation), behavioral attributes and skills (e.g. activity history during adulthood, past exercise program), social and cultural factors (e. g. physician influence, social support from family/friends) and physical environment factors (e. g. access to facilities, climate/season, neighborhood safety) (Trost et al. 2002).

SECULAR TRENDS OF LEISURE-TIME AND OCCUPATIONAL ACTIVITY

The prevalence of regular *exercise* has been shown to increase both among men and women during the last decades (Jacobs et al. 1991; Johansson et al. 1998; Craig et al. 2004). In a Swedish survey on living conditions, the proportion of 16-74 year old men exercising at least once per week, at a level of brisk walking or heavier, has increased since the early eighties (48% in 1980/81, 53% in 1988/89, 56% in 1996/97, and 58% in 1999), but the amount of persons pertaining no exercise at all during leisure-time was constant at around 13% (Johansson et al. 1998; Statistics Sweden 1999). In the U.S. Harvard alumni men, an increase was observed in light and moderate sports, but a decline in vigorous sports from 1962 to 1988 (Lee et al. 1992a). Similarly, an increase in light and moderate intensity leisure-time activities and a decrease in heavy activities were observed in American men from 1974/75 to 1985/87 (Jacobs et al. 1991). When estimating recommended levels of physical activity, defined as moderate-intensity physical activity $\geq$5 times per week for $\geq$30 minutes at each time, or vigorous-intensity physical activity $\geq$3 times per week for $\geq$20 minutes each time, or both during the preceding month, results indicated that leisure-time physical activity trends in the U.S. during the 1990's have remained unchanged (Centers for Disease Control and Prevention 2001). Approximately one fourth of U.S. adults meet recommended levels of physical activity (Centers for Disease Control and Prevention 2001). Prevalence of leisure-time physical *inactivity* was investigated in 35 States in the U.S. between 1988-2002 and inactivity decreased from 29% to 22% during this period among men aged 18- 70 years (Centers for Disease Control and Prevention 2004). Decreasing trends of inactivity over time has also been observed in Finnish men (Barengo et al. 2002) and in Baltimore U.S. men (Talbot et al. 2003) and in Canadian men (Bruce et al. 2002). In a Finnish survey, the proportion of men and women aged 30-59 years with a high *occupational activity* level decreased from 1972 to 1982 (Marti et al. 1988). In the Swedish MONICA project, sedentary occupational levels increased from 1986-1999 in men aged 25-64 years (Lindahl et al. 2003). Although there are publications about some types of physical activity (exercise, leisure-time, as well as inactivity), there is no information available on temporal trends for *total* physical activity in various populations. Due to increasing prevalence of sedentary jobs, labor saving devices in the home and the workplace and motorized transports, total physical activity is expected to have been decreasing over calendar-time.

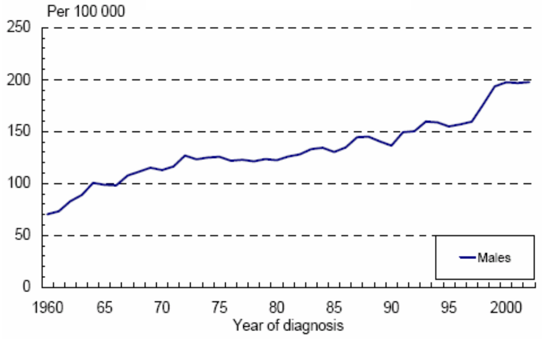


***Figure 1** Trends in prostate cancer incidence*
Source: Official Statistics of Sweden 2003a

Prostate cancer

INCIDENCE AND MORTALITY

Prostate cancer is the third most common cancer among men worldwide, with half a million new diagnoses annually, and is the most common cancer in Western countries (Parkin et al. 2001). The incidence rates of prostate cancer show great variations throughout the world, with an almost hundredfold difference between low-risk populations such as Asia (1.1 per 100,000 per year in China in 1990, world standard age) and high-risk populations such as North America, Northern and Western Europe, and Australia/New Zealand (92.4 per 100,000 in North America in 1990, world standard age) (Parkin et al. 1999). Prostate cancer is the most common cancer among Swedish men. In 2002, 7866 men were diagnosed with prostate cancer, which accounted for 33% of all incident cancer cases in men in Sweden (Official Statistics of Sweden 2003a). In comparison, the world standard age incidence rate in Sweden was 89.5 per 100,000 men in 2002 (Official Statistics of Sweden 2003a). The crude incidence rate was 178 per 100,000 and has been steadily increasing since the 1960's (Figure 1). The crude incidence rate does not take into account the age-structure of the population. Prostate cancer is more common among older men, and in Sweden a larger proportion of the population is older compared to most non-Western countries for instance. This is why the crude rate is much higher compared to the world standard age-adjusted rate in Swedish men. The average annual increase during the last 10 years in Sweden is 3.2% (Official Statistics of Sweden 2003a) and incidence rates are increasing in most parts of the world (Parkin et al. 2001).

In contrast to the increasing incidence rates, age-standardized mortality rates have been quite stable during the last decades in Sweden (Official Statistics Sweden 2003b), which may reflect that an increasing number of prostate cancer cases now is discovered by a test of prostate specific antigen (PSA) in the serum – even if there are no clinical symptoms present (Parkin et al. 2001). PSA testing has increased in Sweden as in many other countries during the last decade although there are no population-based screening programs in Sweden and this probably explains the rapid increase in incidence rates observed (including latent but detectable prostate cancers). Incidence rates may be high in areas where screening examinations are prevalent (e.g. in the USA and in the northern Europe) due to diagnoses of latent cancers (Parkin et al. 2001). In contrast to wide international variations in incidence rates, there is relatively little variation in mortality around the world (Quinn et al. 2002). In Western countries, the rate is around 20 per 100,000 and in Asian countries, the rate is up to 5 per 100,000 (Quinn et al. 2002).

The low fatality means that many men are alive following a diagnosis of prostate cancer. In 2000, an estimated 1.5 million men worldwide were alive at five years after diagnosis, making this the most prevalent cancer in men (Parkin et al. 2001). In Sweden, the corresponding prevalence was 29,000 (Official Statistics of Sweden 2003a). The relative survival rates in Sweden have increased over time and the 10-year rates increased from about 26% in the early 1960's to 45% for men diagnosed in the mid 1990's (Talback et al. 2003).

RISK FACTORS

The causes of prostate cancer are not clearly understood. Both genetic and environmental/lifestyle factors seem to be important (Ross et al. 1996).

Age and ethnicity

Age is a strong risk factor for prostate cancer. Very few cases of prostate cancer is diagnosed in men younger than 50 years, but rates then increase very steeply with age (Quinn et al. 2002). In 2002, 75% of all diagnosed cancer cases in Sweden were in men older than 65 years (Official Statistics of Sweden 2003a). Results from autopsy studies, however, suggest that most men aged 85 years and older have histological prostate cancer (Gronberg 2003). In a study of 500 men in the U.S. who died of trauma, the rate of latent prostate cancer was high at all ages: 30% for men in their 30s, 50% for men in their 50s, and more than 80% for men in their 70's (Sakr et al. 1996).

Ethnicity has been considered a risk factor for prostate cancer. African-Americans have much higher rates compared to Caucasians and the lowest rates are found in Asia (Parkin et al. 1999). High rates are also found in many African countries (Gronberg 2003). The differences between ethnic populations are probably caused by a combination of underlying differences such as genetic susceptibility, exposure to unknown external risk factors, or cancer registration and differences in health care. Migrants from low to high-risk areas of prostate cancer incidence increase their rates of prostate cancer in comparison to the country of origin (Giovannucci 1995; Ross et al. 1996). This change in incidence rate usually takes only one generation to occur, indicating that environmental factors early in life may be of importance.

Family history and genetic susceptibility

Men with a first-degree relative with prostate cancer are at higher risk than men without such a *family history* (Steinberg et al. 1990; Andersson et al. 1996), and it is likely that there is a genetic predisposition for prostate cancer. The importance of *genetic factors* has been pointed out in a study on Scandinavian twins (Lichtenstein et al. 2000) where 42% of the risk was explained by hereditary factors. There are likely to be multiple genes associated with small to moderate risks possibly interacting in complex manners, and possibly interacting with environmental factors, that influence prostate cancer risk (Schaid 2004). Some families may be segregating a gene with high penetrance, but these families are quite rare (Schaid 2004). Family history may also be a risk factor for early age of onset of prostate cancer (Gronberg et al. 1999; Lichtenstein et al. 2000).

Other risk factors

Dietary factors may play an important role in the development and progress of prostate cancer (Kolonel 1996). Ecological and analytical studies have consistently reported positive associations between prostate cancer and consumption of *meat* and *dairy products* (Kolonel 1996; Chan et al. 2001). The direct association between dairy products and prostate cancer has been described by their high content of calcium (Chan et al. 1998a; Giovannucci et al. 1998b). High calcium intake might suppress formation of 1,25 D (Chan et al. 2001); this form of vitamin D has been shown to have anti-tumor capabilities (Skowronski et al. 1993) and prostate cancer growth was inhibited in vitro studies and in animal studies (Lokeshwar et al. 1999).

In a recent review, other dietary factors that might potentially be associated with prostate cancer risk have been discussed (Gronberg 2003). *Selenium* has been suggested to have a protective effect on prostate cancer, as well as *vitamin E* and *lycopene*, the predominant carotenoid in the prostate gland.

Growth and maintenance of the normal prostate epithelium depends on both circulating *testosterone* and the conversion of testosterone to dihydrotestosterone in the prostate (Wilding 1995). Men who underwent castration before puberty and those with congenital abnormalities in androgen metabolism do not develop prostate cancer (Crawford 2003). In animals, testosterone induces prostate cancer tumors (Wilding 1995). Some epidemiological studies support an association between high testosterone and prostate cancer (Gann et al. 1996; Wolk et al. 1997). High levels of circulating testosterone and low levels of sex hormone-binding globulin (SHBG) were associated with increased risk of prostate cancer in a nested case-control study within the Physicians Health Study (Gann et al. 1996) and also in a population-based case-control study in Sweden (Wolk et al. 1997).

Insulin-like growth factor I (IGF-I) regulates proliferation, differentiation, and apoptosis of cancer cells (Yu et al. 2000). High concentrations of circulating IGF-I were associated with increased risk of prostate cancer in nested case-control studies within prospective cohorts (Chan et al. 1998c; Stattin et al. 2000) and also in population-based case-control studies (Wolk et al. 1998) (Oliver et al. 2004). Oliver and coworker studied PSA-screen-detected prostate cancers and observed a stronger association between IGF-I and advanced cancers (Oliver et al. 2004).

There is no strong support for an association between *body mass index* (BMI, kg/m^2) and prostate cancer, but recent results from epidemiologic studies suggest that a high BMI is associated with prostate cancer (Calle et al. 2003). In a prospective study of 400,000 men where 4,000 men died from prostate cancer, men with a BMI of 35.0 to 39.9 had a 34% greater risk of dying of prostate cancer than those with a normal BMI of 25.0 and lower (Calle et al. 2003). A positive association between body size and prostate cancer has also been observed in a prospective cohort of 135,000 construction workers where 2,300 men were diagnosed with prostate cancer during 20 years of follow-up (Andersson et al. 1997). A possible mechanism could be that obese men have lower levels of sex hormone-binding globulin (Siiteri 1987) and therefore levels of free testosterone are increased. Moreover, elevated levels of IGF-I have been observed in obese subjects (Crawford 2003).

Smoking and *alcohol* do not seem to be important risk factors for prostate cancer, although only few studies have been conducted (Crawford 2003).

PHYSICAL ACTIVITY

Previous studies

Physical activity has been studied as a modifiable risk factor that may reduce the incidence of prostate cancer. Epidemiological studies play an important role in assessing the relationship between physical activity and prostate cancer. Physical activity level has been estimated by measuring time spent in sports, leisure or occupational activity and at least 34 cohort and case-control studies have investigated the relation between physical activity and prostate cancer, but results are inconclusive (Lee et al. 2001b; IARC 2002). Almost half of the studies report a statistically significant association between low levels of physical activity and increased prostate cancer risk (Paffenbarger et al. 1987; Vena et al. 1987; Albanes et al. 1989; Brownson et al. 1991; Dosemeci et al. 1993; Hsing et al. 1994; Thune et al. 1994; Oliveria et al. 1996; Hartman et al. 1998; Villeneuve et al. 1999; Bairati et al. 2000; Clarke et al. 2000; Wannamethee et al. 2001). In most of these studies, the observed increased risks for the least active group compared to the most active group range between 20% to 90% (Hsing et al. 1994; Clarke et al. 2000). In one case-control study the observed relative risk was 5.0 for men with a sedentary job compared to those with a physically active job (Dosemeci et al. 1993). Some studies report a non-statistically significant association (Yu et al. 1988; Severson et al. 1989; Lee et al. 1994; Andersson et al. 1995; Steenland et al. 1995; Will et al. 1999; Lund Nilsen et al. 2000) between low levels of activity and prostate cancer, others do not observe any association at all (Lee et al. 1992b; Whittemore et al. 1995; Giovannucci et al. 1998a; Liu et al. 2000; Pukkala et al. 2000; Putnam et al. 2000; Lee et al. 2001a) and in contrast, positive associations have been observed in seven studies (Polednak 1976; Le Marchand et al. 1991; West et al. 1991; Ilic et al. 1996; Cerhan et al. 1997; Sung et al. 1999; Lacey et al. 2001). Furthermore, results have differed within the same study for different types of activities, for instance for occupational activity vs. leisure-time activity (Villeneuve et al. 1999; Clarke et al. 2000).

Biological plausibility

An association between physical activity and prostate cancer is biologically plausible and has been postulated by different possible mechanisms, but no definite mechanisms have been identified.

Physical activity may protect against the development of prostate cancer through reduction of endogenous levels of *sex hormones*, particularly *testosterone*. Several lines of evidence support a role for androgen sex hormones as initiators or promoters of prostate cancer. Growth and maintenance of the normal prostate epithelium depends on both circulating testosterone and the conversion of testosterone to dihydrotestosterone in the prostate (Wilding 1995). It has been hypothesized that androgens may not be involved in prostate cancer initiation, but that an altered hormone metabolism may play a role in the progression of prostate cancer from histologic to clinically significant forms (Friedenreich et al. 2001). While testosterone levels may be acutely elevated following a session of aerobic exercise (Zmuda et al. 1996; Fahrner et al. 1998; Strüder et al. 1998), several studies have reported lower basal serum levels of testosterone in athletically trained men relative to untrained men (Wheeler et al. 1984; Smith et al. 1993; Strüder et al. 1998). When inducing testosterone production by infusing gonadotrophin-releasing hormone (GnRH), a significantly lower testosterone production was observed in trained men compared to sedentary men (Hackney et al. 2003). Sex hormone binding globuline (SHBG), which binds testosterone and thus reduces the levels of free testosterone, has been positively associated with physical activity (Barnard et al. 2002). Increased levels of SHBG were observed immediately after exercise in older men (Zmuda et al. 1996) and after an exercise program in obese men and athletes (Caballero et al. 1992; Tymchuk et al. 1998).

The mitogenic and antiapoptotic properties of *insulin-like growth factor I* (IGF-I) may influence carcinogenesis of the prostate. Higher levels of IGF-I were associated with increased risk of prostate cancer (Wolk et al. 1997; Chan et al. 1998c; Stattin et al. 2000) and might also be associated with physical activity levels but results are conflicting (Yu et al. 2000). Inconsistent findings may be age-related; exercise seems to decrease IGF-I levels in children and adolescents (Eliakim et al. 1998) and increase levels in adults (Bermon et al. 1999; Yu et al. 2000).

The *immune system* is involved in regulating the susceptibility to both initiation and promotion of tumors, and can be modified by physical activity (Shephard et al. 1995). Depending on intensity, duration and frequency of activity, immune functions can be suppressed or enhanced by physical activity, but moderate physical activity usually stimulates the immune response. An increase in the number of natural killer cells and/or their activity following acute exercise has been observed (Mackinnon 1989).

Physical activity might be associated with lower prostate cancer risk through its role in controlling *body weight*. Recent studies support the positive association between obesity and increased prostate cancer risk (Andersson et al. 1997; Calle et al. 2003; Crawford 2003), although earlier findings have been inconsistent. Body mass may influence serum androgen concentrations (Mantzoros et al. 1995), possibly by decreasing levels of sex hormone-binding globulin (Siiteri 1987; Barnard et al. 2002) and therefore increasing free testosterone levels and/or by elevating IGF-I levels (Crawford 2003).

AIMS

The aims of the thesis were

- To evaluate the validity and reproducibility of self-reported total physical activity and different types of activities among men

- To study if total physical activity levels change with age and lifestyle factors such as body mass, smoking, educational level, marital status, and self-rated health

- To estimate changes in levels of total physical activity and different types of activities among men over calendar time – trends during 1930's to 1990's

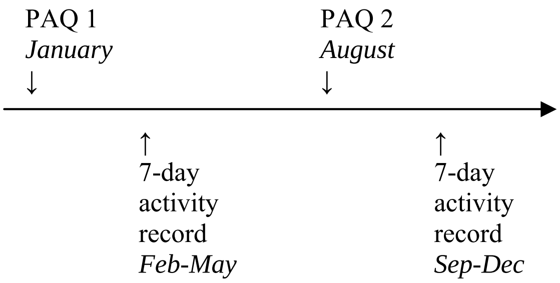
- To study if occupational physical activity is associated with prostate cancer risk

STUDY DESIGN, POPULATION AND METHODS

Study design and population

VALIDITY OF A PHYSICAL ACTIVITY QUESTIONNAIRE (PAPER I)

We evaluated the validity and reproducibility of a short self-administered physical activity questionnaire intended to measure total daily physical activity. To assess reproducibility of the physical activity questionnaire, it was mailed to participants twice in 1998 (January and August). To determine the validity of the questions we used two 7-day activity records as the reference method, mailed one week after they returned a completed questionnaire (Figure 2).



PAQ - Physical Activity Questionnaire

Figure 2 *Study design (paper I)*

To the present validation study, we invited 286 men (aged 44-78 years) from central Sweden (Uppsala and Knutby), who had been previously randomly selected and participated in a validation study of a self-administered food frequency questionnaire in 1994-96 (Messerer et al. 2004). Among the invited men, 224 filled in the first questionnaire and 222 filled in the second questionnaire. In the analyses, we included 111 men who completely filled in the first questionnaire and recorded their physical activity for one or two weeks.

POPULATION TRENDS OF PHYSICAL ACTIVITY (PAPER II-III)

To study if total physical activity and different types of activities were associated with age and some lifestyle factors and calendar-time, a population-based prospective cohort of Swedish men (COSM) including 48,645 subjects living in central Sweden (Västmanland and Örebro Counties) was established during the autumn of 1997 and winter/spring of 1998. An invitation to participate in the study along with a questionnaire about physical activity (the validated physical activity questions in paper I), diet and other lifestyle behaviors was mailed to all 100,303 men aged 45-79 years, living in the study area in 1997 and the response rate was 48%. The men and their addresses were identified through the population registers in the counties. In the analyses, we included 33,466 men (the study cohort) with complete information on all six questions about current physical activity and the covariates.

OCCUPATIONAL PHYSICAL ACTIVITY AND PROSTATE CANCER RISK (PAPER IV)

The association between occupational physical activity and prostate cancer risk was investigated using the Cancer-Environment Register 60/70 (CER60/70), which was created by linking the Swedish census data with the national Swedish Cancer Register by the individually unique ten-digit national registration number that is assigned to all Swedish inhabitants.

Nation-wide Swedish Census

Since 1960, census information has been obtained regularly in Sweden, using questionnaires mailed to every household. The questionnaires cover demographic, occupational (including employment status, job title, industry and work address), and socio-economic factors for each household member and focus on the status during one specified week in October (Official Statistics of Sweden 1975). Stored with the data is the national registration number – a unique personal identifier assigned to all Swedish residents – that permits linkage between registers. Since participation is mandatory by law, and since great efforts are made to trace non-responders, the censuses are more than 99% complete (Official Statistics of Sweden 1965; Official Statistics of Sweden 1974).

Swedish Cancer Register

The national Swedish Cancer Register, established in 1958, covers more than 98% of all diagnosed cancer cases in the country (Mattson 1977). It contains demographic information and detailed tumor data - site (coded according to ICD-7) and histopathology codes, date and mode of diagnosis but no information on tumor stage. The Cancer Register is linked annually to the Swedish Register of Causes of Death, which provides information on dates of death for deceased and the underlying and contributing causes of death derived from the obligatory death certificates (Statistics Sweden 1991). The proportion of prostate cancer that was histopathologically verified was 96-99% during the period 1971-1989 (Official Statistics of Sweden 1983; Official Statistics of Sweden 1992a).

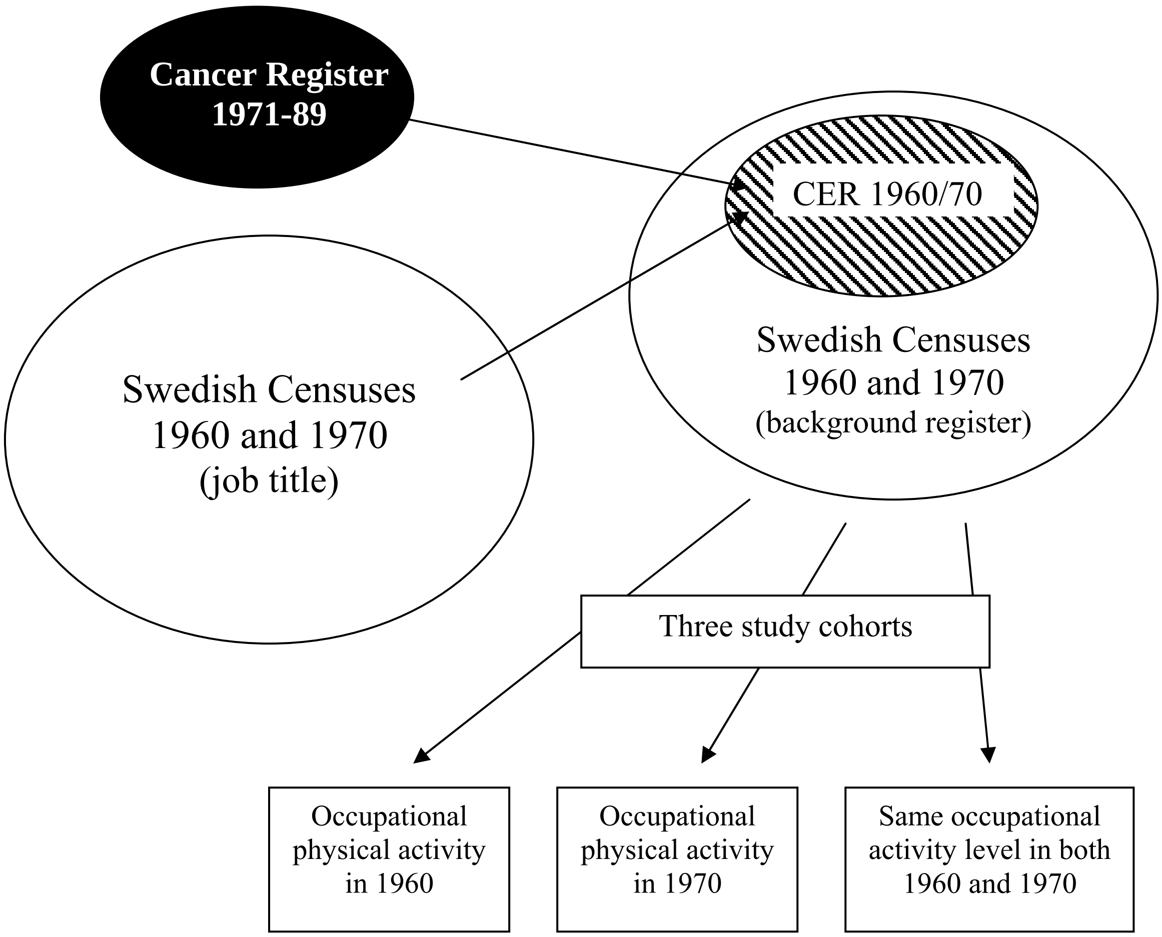


Figure 3 *Cancer Environment Register 1960/70 (CER 1960/70) (Paper IV)*

Cancer-Environment Register

The Cancer–Environment Register 1960/70 (CER60/70) was established in 1994 by linking Cancer Register data from 1971 through 1989 to the census data from 1960 and 1970, using the national registration numbers as identifiers (Figure 3) (Centre for Epidemiology 1994). The CER60/70 proper thus includes cancer patients whose cancer was diagnosed during 1971-1989 and who resided in Sweden both in 1960 and 1970 along with their census data.

For comparison to the CER60/70 proper, there is a background register with *all* Swedish residents who took part in both the 1960 and 1970 censuses (Figure 3). Except for tumor data, the information in this background register is the same as in the CER60/70 proper, including dates (but not causes) of death for the deceased. The background register included 3,283,493 men aged 16 to 110 years in 1971. After record linkages, the national registration numbers were removed from both the CER60/70 proper and the background register to ensure confidentiality.

Study Cohorts

A total of 1,348,971 men in the background register reported employment in the 1960 census and had a job that we could classify with regard to physical activity. There were 1,377,629 men with such classified jobs in 1970. From the overlap of these two groups of men, we further identified the 673,443 men who had jobs requiring the *same* physical activity level both in 1960 and 1970 censuses (Figure 3). Around 20% of all men reported no occupation in 1960 and 1970, and four %of cases in 1960 and 38% of cases in 1970 reported no occupation. Older men were more likely to have reported the same occupation both in 1960 and 1970 compared to younger men (Centre for Epidemiology 1994).

To ascertain prostate cancer incidence and dates of diagnosis in these three cohorts, we linked the background register to the CER60/70 proper, matching on all variables that these both data sets had in common. Prostate cancers diagnosed incidentally first at autopsy were excluded from analyses. Person-years were calculated from January 1, 1971 until the diagnosis of prostate cancer, death, or end of follow-up (December 31, 1989), whichever occurred first. During follow-up, 62,124 prostate cancer cases were diagnosed in the study.

Assessment of physical activity

TOTAL PHYSICAL ACTIVITY AND DIFFERENT TYPES OF ACTIVITIES (PAPER I-III)

Physical activity questionnaire (Paper I-III)

Total daily 24-hour physical activity was assessed using a short self-administered questionnaire. Information on usual average physical activity/inactivity during the previous year and recalled for the ages 15, 30 and 50, was collected using five questions with predefined response categories and one open question (Figure 4). There was also one open question about hours per day of sitting/lying.

The 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. 1993). For the questionnaire, we used mean MET values based on specific activities within corresponding categories (Figure 4). For the question about sitting/lying, we used intensity level of 1.3 MET. Physical activity levels (MET-hours) for specific activities were estimated by multiplying reported *time* (h) by *MET* ($kcal \cdot kg^{-1} \cdot h^{-1}$). Energy expenditure (kcal) can be estimated by multiplying MET-hours with individual weight (kg).

Based on the questionnaire data, we estimated both the *crude* total physical activity (Paper I), and a total *activity score* (Paper I-III). The first, *crude* total activity level, was based directly on the self-reported data, by adding the specific activities together (except sitting/lying). For the second, total *activity score*, 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. Four men in the validation study reported more than 24 hours of daily activities, ranging from 24.1 to 26.4 hours, and this time was multiplied by 2.0 MET and subtracted from the total. We refer to the activity category during the correction time as "other". We estimated a *non-occupational activity score* by excluding work/occupational activity level from the total activity score in Paper II-III.

The questionnaire used in the validation study also inquired about current weight and height and the questionnaire used in the cohort of men (paper II and III) also inquired about weight and smoking at age 15, 30, 50, as well as education, marital status and self-perceived health. There were predefined levels of education, marital status and health. We computed body mass index (BMI = weight(kg)/ height(m)^2) as a measure of obesity at different ages.

Physical activity records – the reference method for validation (Paper I)

A self-administered structured 7-day physical activity 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 (Figure 5). Participants recorded the clock time they started and the time they finished the activity and described all their activities (for example sitting, eating, walking, 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. Study subjects also recorded the number of stair flights climbed every day.

Mark your level of physical activity **at different ages**:

	15 yrs	30 yrs	50 yrs	this yr	*Assigned mean MET values* [a] (*not shown in the questionnaire*)
Work/occupation [b]					
Mostly sitting down	☐	☐	☐	☐	*1.3*
Sitting down half the time	☐	☐	☐	☐	*1.8*
Mostly standing up	☐	☐	☐	☐	*2.2*
Mostly walking, lifts, carry little	☐	☐	☐	☐	*2.6*
Mostly walking, lifts, carry much	☐	☐	☐	☐	*3.0*
Heavy manual labour	☐	☐	☐	☐	*3.9*
Walking/bicycling					*3.6*
Hardly ever	☐	☐	☐	☐	
Less than 20 min/day	☐	☐	☐	☐	
20-40 minutes/day	☐	☐	☐	☐	
40-60 minutes/day	☐	☐	☐	☐	
1-1,5 hours/day	☐	☐	☐	☐	
More than 1,5 hours/day	☐	☐	☐	☐	
Home/household work					*2.5*
Less than 1 hour/day	☐	☐	☐	☐	
1-2 hours/day	☐	☐	☐	☐	
3-4 hours/day	☐	☐	☐	☐	
5-6 hours/day	☐	☐	☐	☐	
7-8 hours/day	☐	☐	☐	☐	
More than 8 hours/day	☐	☐	☐	☐	
Leisure-time					
Watching TV/reading					*1.2*
Less than 1 hour/day	☐	☐	☐	☐	
1-2 hours/day	☐	☐	☐	☐	
3-4 hours/day	☐	☐	☐	☐	
5-6 hours/day	☐	☐	☐	☐	
More than 6 hours/day	☐	☐	☐	☐	
Exercise					*5.0*
Less than 1 hour/week	☐	☐	☐	☐	
1 hour/week	☐	☐	☐	☐	
2-3 hours/week	☐	☐	☐	☐	
4-5 hours/week	☐	☐	☐	☐	
More than 5 hours/week	☐	☐	☐	☐	

How many hours of each 24-hour day do you usually sleep? *0.9*

☐ Hours

Figure 4 *Physical activity questionnaire and assigned mean MET values*

a Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71-80.

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).

Date: 980202 ACTIVITY RECORD DAY 1

Personalnumber: 211221–22XX

x - slow *xx - medium* *xxx - fast/brisk* *xxxx - very fast/brisk*

From	*To*	*Activity/occupation*	*Intensity*
00.00	06.45	Sleeping	
06.45	06.49	Fetching newspaper	
06.49	07.11	Laid down, reading	
07.11	07.20	Getting dressed	
07.20	07.40	Made breakfast, sat eating	
07.40	07.55	Walked the dog	X X X
07.55	08.05	Standing/walking at home	
08.05	08.18	Driving car to work	
08.18	09.25	Standing/walking at work	
09.25	10.15	Sitting at work, paper work, coffeebreak	
10.15	11.50	Walking at work, carrying light things	X
11.50	11.58	Walking to lunch cafeteria	X X
11.58	12.40	Sitting, eating	
12.40	12.50	Walking	X X
12.50	14.10	Sitting, meeting	
14.10	---		
---	23.00		
23.00	24.00	Sleeping	

Check a box each time you walk upstairs. One box per floor!

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

E X A M P L E

Figure 5 *An example of an activity record*

All activities recorded were assigned specific MET values taking into account the intensity level when appropriate (Ainsworth et al. 1993). Every flight of stairs climbed was assigned 10 seconds and 5.0 MET. Then, to make comparison with the questionnaire possible in the validation study (Paper I), all the recorded activities were classified into one of the seven activity groups inquired in the questionnaire. Activities such as gardening, home repair, and fishing/hunting in the records were classified into the "work/occupation" category. Recorded activities that did not fit into any of the categories asked for in the questionnaire were self-care, walking at home, sitting eating, driving etc. This category was classified as "other". The estimates of the average total daily physical activity and the seven activity groups were computed by summarizing MET-hours for all specific activities.

Table 1 *Classification of men by occupational physical activity, based on occupational codes in census data from 1970*

Level of physical activity	Occupation	Freq (%)
Very high /high	General farmers; specialized farmers; forestry workers	39
	Carpenters, joiners and parquetry workers	16
	Dockers and freight handlers	13
	Loggers; forestry workers	10
	Other	22
Medium	Carpenters and related woodworkers	16
	Building caretakers	8
	Material handling equipment operators not elsewhere classified	8
	Stock clerks	7
	Other	61
Light	Civil engineers, industrial engineers, civil engineering technicians and related workers	36
	Commercial travelers and manufactures agents; managers (wholesale and retail trade); sale supervisors; buyers and related workers	10
	Working proprietors (wholesale and retail trade)	4
	Compositors and type-setters; printing pressmen and related workers	4
	Other	46
Sedentary	Production managers, general managers and related workers	32
	Book-keepers	9
	Chemical engineers and related workers	8
	Personell and occupational specialists; managers not elsewhere classified	6
	Other	45

OCCUPATIONAL PHYSICAL ACTIVITY (PAPER IV)

Occupations reported in nation-wide census questionnaires were coded, using a three-digit classification devised by the National Labor Market Board in Sweden, into 245 categories in the 1960 and 248 categories in the 1970 census (Official Statistics of Sweden 1975).

Three Swedish specialists in occupational medicine, working independently, classified each occupational category as very high, high, moderate or light physical activity or sedentary. We considered only occupations consistently classified by the three experts, to reduce misclassification; we required agreement between at least two of the raters while the third was allowed to diverge by no more than one category (Table 1). A total of 202 occupations were thus unequivocally classified (Moradi et al. 1998). In both 1960 and 1970, 24% men with a job code were unclassified. Because few men were classified as having jobs with very high physical demands, the two categories of highest physical activity – very high and high – were combined, resulting in four categories.

Statistical analyses

VALIDITY OF A PHYSICAL ACTIVITY QUESTIONNAIRE (PAPER I)

To describe the distribution of physical activity in the validation group of 111 men, medians and interquartile ranges were computed together with means, because some variables were not normally distributed. Mean and standard deviations (SD) were computed to describe the distribution of age and body mass index.

To compare levels of activity between questionnaires and records, statistical tests for dependent samples were used. To test reproducibility of the questionnaire, we compared the first and the second questionnaire using two ways of calculating physical activity (crude and total activity score), as well as for specific types of physical activity. To test validity, the questionnaire was compared with the records. We present results from the first questionnaire only, because results for the second questionnaire might be influenced by the process of recording physical activity in the activity records. We used Pearson and Spearman correlation and results for these two tests were in general similar. However, we decided to show Spearman correlation, since some variables were not normally distributed. To study the agreement between the two assessments we used concordance correlation (Lin 1989). This test measures the variation from the 45° line through the origin, since standard correlation methods correlation fail to detect any departure from the 45° line, and only estimates the association. To adjust for within- and between-person variability in the activity records, we deattenuated the Spearman correlations using the methods of Beaton (Beaton et al. 1979) and Liu (Liu et al. 1978). To estimate the within-person and between-person variance, we used a one-way random effects ANOVA model based on data from men who had completed all 14 days of activity recording. To adjust for an underestimation of the observed validity correlation coefficient (in the validation study) due to random error decreasing the reproducibility of the physical activity questionnaire, we divided the observed correlation between the questionnaire and the records by the square root of the reproducibility correlation of the questionnaire (Armstrong et al. 1992).

We evaluated reproducibility and validity of the questionnaire in subgroups of age (< 65 and ≥ 65 years) and BMI (≤ 26.0 and > 26.0 kg/m^2). Cutoff levels were chosen with regard to the medians in the study group. Correlation coefficients between subgroups were compared by normal tests after Z transformation at 5% significance level.

POPULATION TRENDS OF PHYSICAL ACTIVITY (PAPER II-III)

The distribution of the total physical activity scores was slightly skewed; therefore a log transformation was applied to improve symmetry and approach normality. All intercepts shown are anti-logged for easier interpretation.

In the cross-sectional analyses (paper II), we used a multiple linear regression model to study the simultaneous relation between physical activity, as reported at baseline, and current age, BMI, smoking status, marital status, educational level and self-rated health. Current age was grouped in seven categories (45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 years), whereas BMI was grouped in three classes (<25, 25-<30, ≥30 kg/m^2). The lowest levels of the categorized variables as for the other variables were used as reference groups.

The longitudinal change in physical activity (paper III) in individuals at age 15, 30 and 50, and its association with BMI and smoking status at respective age, and educational level was analyzed using a random effect model (Diggle et al. 1994), with each person contributing up to three observations. Age at baseline (in 1997) was included in the models to take into account changes in physical activity depending on "generation", or differences in reporting attributable to age using the same categorization as above. A random "intercept" was considered for the subject-specific error.

Time trends of change in total physical activity (paper III) and subtypes of activities over calendar time were studied separately for men at age 15, age 30 and age 50, adjusted for BMI and smoking at respective age and education, in a linear regression model. Due to the small number of possible values for the different types of activities, including 0 for walking/bicycling and exercise, linear regression were more appropriate on the natural scale.

OCCUPATIONAL PHYSICAL ACTIVITY AND PROSTATE CANCER RISK (PAPER IV)

We estimated the risk of prostate cancer in relation to occupational physical activity by performing internal comparisons between different exposure groups within the cohorts. To compute the relative risk (RR), we fitted Poisson models by the maximum likelihood method, assuming that the log Poisson rate was a linear function of the covariates, (Preston et al. 1995). The very high/high activity group was larger than sedentary activity group and was chosen as the reference category. The baseline model was adjusted only for age at follow-up. Data were analyzed in grouped form. Attained age (age at follow-up) was divided into nine 5-year categories (<50, 50-54, ..., 80-84, 85+ years). The nineteen calendar years of follow-up were divided into three 5-year intervals and one 4-year (January 1, 1971 - December 31, 1975, 1976-1980, 1981-1985, 1986-1989). The second model was further adjusted for calendar year of follow-up and place of residence. We adjusted for calendar year of follow-up to take into account any differences in diagnostic routines for prostate cancer over the time period. Place of residence is associated with overweight and fruit/vegetable and meat/dairy consumption in Sweden (Table 2). These exposures have been considered as risk factors for prostate cancer (Chan et al. 1998b). Place of residence has been associated with prostate cancer risk in a Swedish study (Andersson et al. 1995). Place of residence was obtained from the census data and categorized into six levels: (Stockholm – capital; Gothenburg and Malmö – second and third largest cities in Sweden; other large municipalities; southern and central Sweden (except the cities and large municipalities); northern densely populated areas; northern sparsely populated areas) (Öberg et al. 1991).

The model was further adjusted for socio-economic status. Socio-economic status is associated with some factors that have been considered as risk factors for prostate cancer (Table 2). We categorized socio-economic status into six levels according to Swedish classification (unskilled and semi-skilled workers, skilled workers, junior salaried employees, intermediate-level and senior salaried employees, farmers, and entrepreneurs), based on the occupational title in the census data (Official Statistics of Sweden 1995). In stratified analyses, the association between physical activity and prostate cancer relative risk was investigated for different age groups (age at follow-up) and socio-economic status. Trends in relative risk were tested with the scores (high, medium, low, and sedentary) equally spaced.

Table 2 *Percentage of overweight persons in Sweden 1988-89[a]. Average food expenditure in 1989[b]*

	Overweight [c] (%)	Fruit and vegetables [d] (kg/person/year)	Meat and dairy products [e] (kg/person/year)
Place of residence			
Stockholm	30	109	188
Gothenburg and Malmö	36	99	178
Large municipalities	38	95	186
Southern and central Sweden	40	94	209
Northern densely populated areas [f]	36		
Northern sparsely populated areas [f]	46	88	229
Socioeconomic status			
Unskilled blue-collar workers [g]	40	84	195
Skilled blue-collar workers [g]	42		
Farmers	52	83	263
Entrepreneurs	47	97	182
Junior salaried employees	37	100	198
Intermediate-level and senior salaried employees	34	103	191

a Data from Official Statistics of Sweden 1991
b Data from Official Statistics of Sweden 1992
c Overweight defined as body mass index >25.0 kg/m^2, men only
d Including household production, men and women together
e Men and women together
f Northern densely populated areas and Northern sparsely populated areas analyzed together for average food expenditure
g Unskilled blue-collar workers and skilled blue-collar workers analyzed together for average food expenditure

Validity of a physical activity questionnaire (Paper I)

The mean age and standard deviation of the study participants in the validation study was 63.2 (9.3) years and the mean BMI was 25.8 (3.2) kg/m^2.

TOTAL PHYSICAL ACTIVITY

Table 3 shows medians, interquartile ranges and correlations for total daily activity (MET-hours) and daily energy expenditure (kcal) based on the questionnaire and records in the validation group. Validity of the *total activity score*, measured as correlation with the records, was higher compared to the *crude total activity* level, i.e. the total activity score better ranked subjects.

The total activity score from the questionnaire is plotted against the records in Figure 6. Questionnaire-based total activity score overestimated total activity level per day by 5% on the records (p<0.01) and crude scores were underestimated by 22% (p<0.01). Correlations for energy expenditure were higher than for physical activity scores (Table3).

Table 3 *Total daily physical activity and energy expenditure, based on the questionnaire (PAQ) and on the activity records, in the validation group of 111 men*

	Daily activity/expenditure Median (interquartile range)			Spearman correlation [a] Validity		Reproducibility
	PAQ 1 winter/spring	PAQ 2 summer/fall	Records [b]	PAQ 1 vs Records [b] [c]	[d]	PAQ 1 vs PAQ 2
PHYSICAL ACTIVITY, MET-hours/d						
Crude total activity [e]	30.6 (9.2)	28.3 (8.3)		0.23	0.29	0.65
Total activity score [f]	40.8 (5.8)	40.3 (6.5)	39.0 (5.5)	0.56	0.69	0.65
ENERGY EXPENDITURE, kcal/d						
Crude total activity [e]	2377 (809)	2251 (891)		0.55	0.63	0.75
Total activity score [f]	3294 (676)	3378 (710)	3107 (688)	0.81	0.89	0.83

a All correlations significant at 5% significance level
b Up to fourteen days of records (7/14 days); 75 of 111 men with 14 days
c Deattenuated Spearman correlation, adjusted for within- and between-person variation in the records
d The correlation further adjusted for reproducibility of the questionnaire
e Based directly on self-reported data
f Based on self-reported data, corrected to 24 hours

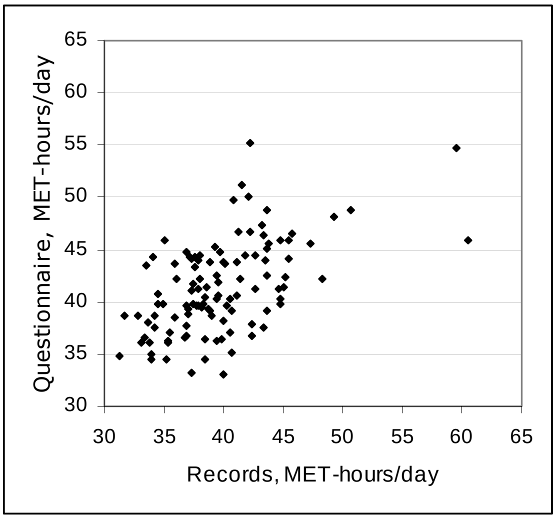


Figure 6 *Plot of total physical activity score from questionnaire against activity records*

Spearman correlations did not differ substantially in a subgroup of 68 men who completed both first and second questionnaire as well as both 7-day activity records (r=0.50 for validity, r=0.65 for reproducibility). Spearman correlations for reproducibility of the total activity score at ages 15, 30 and 50 in the validation group were 0.80, 0.78 and 0.82, respectively, and median and interquartile ranges were 43.5 (9.3), 43.4 (8.6), and 42.4 (8.6).

We estimated a *non-occupational activity score* by excluding occupational activity from the total activity score. Median activity score and interquartile range for the questionnaire and the record was 29.7 (2.4) and 28.0 (4.8) MET-hours/day respectively. Spearman correlation coefficient between the first physical activity questionnaire and the records was 0.31 and the reproducibility coefficient was 0.62. Spearman correlations for reproducibility of the non-occupational activity score at ages 15, 30 and 50 were 0.64, 0.55 and 0.72, respectively.

SPECIFIC ACTIVITIES

The distribution of different activities over 24 hours is shown in Figure 7. Spearman correlations for specific activities ranged between 0.59 (exercise) and 0.76 (sleeping) for reproducibility and between 0.22 (exercise) and 0.78 (home/household work) for validity as shown in Table 4. In the validation group, 17% reported less than one hour of exercise per week in the first questionnaire (winter/spring), but 57% did not record any exercise in the diaries (both seasons).

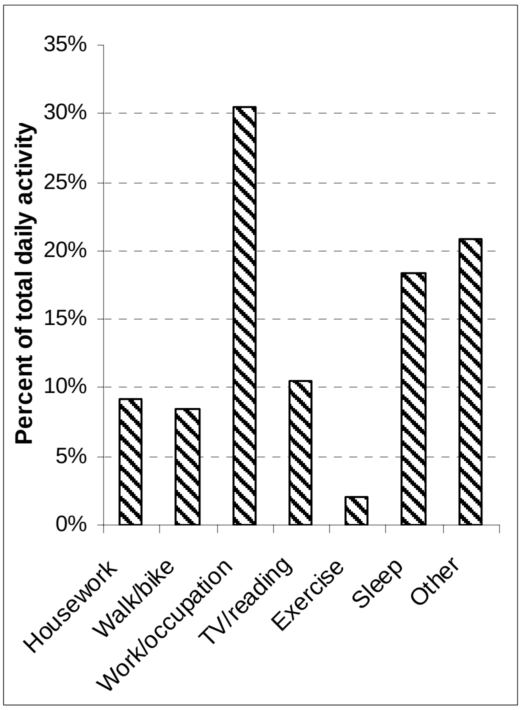


Figure 7 *Proportion of specific activities (MET-hours) during 24 hours based on activity records*

The median of the question about sitting/lying (which was not included in the total activity score) was 7.8 MET-hours/day in the questionnaire (interquartile range 9.1) and 13.2 MET-hours/day in the activity records (interquar-

Table 4 *Physical activity by type of specific activities, based on the questionnaire (PAQ) and the activity records, in the validation group of 111 men*

	Spearman correlation	
	Validity[a]	Reproducibility[b]
Work/occupation	0.49	0.68
Home/household work	0.78	0.64
Walking/bicycling	0.39	0.47
Exercise	0.22	0.59
TV/reading	0.63	0.68
Sleeping	0.70	0.76
Other	0.27	0.72
Combined walking/bicycling + exercise	0.49	0.68

a PAQ1 vs records (up to 14 days), adjusted for within- and between person variation in the records and for reproducibility of the PAQ
b PAQ1 vs PAQ2
c For example sitting (transportation, eating), walking at home, self-care

Table 5 *Total physical activity based on the questionnaire and on the activity records, in the validation group of 111 men, by age and body mass*

	Spearman correlation		
	Validity		Reproducibility
	PAQ1[a] vs Records[b] c	d	PAQ1 vs PAQ2
AGE (yrs)			
44-64	0.65	0.77	0.72
65-78	0.50	0.68	0.54
BMI (kg/m^2)			
≤26.0	0.73	0.87	0.70
>26.0	0.39	0.50	0.60

a PAQ, physical activity questionnaire, total activity score
b Up to fourteen days of records (7/14 days); 75 of 111 men with 14 days
c Deattenuated Spearman correlation, adjusted for within- and between-person variation in the records
d The correlation further adjusted for reproducibility of the questionnaire

tile range 3.4). Spearman correlation coefficient between the first questionnaire and the records was 0.36 for this question when adjusting for within- and between-person variation in the records, and 0.75 when further adjusting for random error in the questionnaire. We changed the question about sitting/lying in the second questionnaire slightly by adding "do not include sleep", and the reproducibility coefficient between the first and the second questionnaire was 0.26.

SUBGROUPS OF AGE AND BMI

The older age group (65-78 years) significantly overestimated their median absolute physical activity in the questionnaire, compared to records ($p<0.01$). Correlations for validity and reproducibility were non-significantly higher in the younger age group (44-64 years) compared to the older men (Table 5). There was no difference in BMI between the two age groups ($p=0.60$).

In both BMI groups, the absolute physical activity levels were significantly overestimated ($p<0.01$) in comparison to the records. Correlations for validity, but not for reproducibility, were significantly higher ($p<0.05$) in the lower (≤26.0 kg/m^2) than in the higher BMI-group (>26.0 kg/m^2) (Table 5). There was no statistically significant difference in age between the two BMI-groups ($p=0.59$).

Population trends of physical activity (Paper II-III)

Our study cohort used for trend analyses of physical activity, including 33,466 men aged 45-79 years, well represents the Swedish male population regarding age composition, relative weight and educational level (Table 6) (Official Statistics of Sweden 1999, Johansson et al. 1998).

Table 6 *Comparison of our study cohort with the Swedish population and a Swedish national survey on living conditions, regarding age composition, overweight and education*

	Study cohort N= 33,466	Swedish population[a] 45-79 yrs	Survey on living conditions[b]
AGE			
45-64 yrs	66%	68%	
65-79 yrs	34%	32%	
OVERWEIGHT[c]			
45-64 yrs	58%		59%
65-79 yrs	54%		52%
COLLEGE EDUCATION			
45-64 yrs	21%	23%	
65-79 yrs	11%	13%	

a Official Statistics of Sweden 1999
b Johansson et al. 1998
c BMI ≥ 25kg/m^2

The study cohort is also similar to the population in the validation group of 111 men (Paper I). There were no statistically significant differences in BMI, proportion of smokers or total physical activity score between these two groups (p>0.05), but the validation group was older compared to the cohort (mean of 63 years vs. 61 years, p=0.02).

Physical activity by age - cross-sectional analysis (Paper II)

Median and interquartile ranges in the study cohort were 40.8 (7.0) for total activity and 29.6 (2.8) for non-occupational activity in MET-hours/day. Work/occupational activity level in the study cohort accounted for 27% of the total activity.

Total daily activity score at baseline was 4.1% (95% CI: -4.6, -3.6) lower in the oldest age group (75-79 years) compared to the youngest age group (45-49 years) in multivariate analyses, when adjusting for BMI, smoking, education, marital status and self-rated health and the intercept was 43.3 MET-hours/day. Self-rated health was the most important explanatory variable for total activity score followed by education. Men who reported poor/very poor health had 10% lower total activity level compared to men with good self-rated health. College educated men had 7% lower total activity level compared to low-educated men. When excluding work/occupational activity from the total activity score (non-occupational activity), the association between activity and education disappeared.

The association of age with total physical activity was modified by BMI, smoking, education and self-rated health. The inverse association with age was apparent in all subgroups, but was strongest among obese men, current smokers, low-educated men and men who reported poor/very poor health (Figure 8).

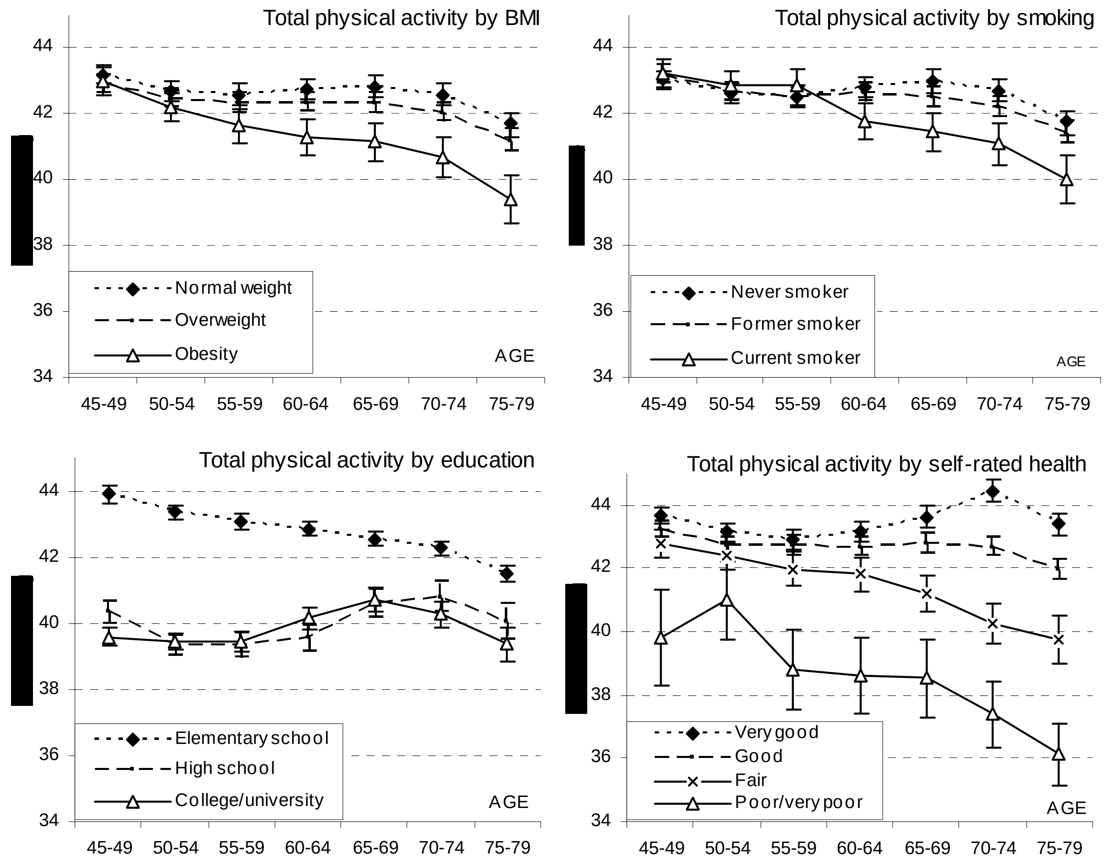


Figure 8 *Cross-sectional age-dependent differences in total daily activity by BMI, smoking education, and self-rated health adjusted for BMI, smoking, education, marital status and self-rated health, when appropriate*

LONGITUDINAL CHANGES IN PHYSICAL ACTIVITY BY AGE (PAPER III)

Median (interquartile range) total daily activity scores among men that retrospectively estimated their activity at age 15, 30 and 50 years, were 44.2 (8.1), 43.4 (9.1), and 41.5 (7.5) MET-hours/day, respectively. Total activity decreased with 1.6% from age 15 to 30 and 3.9% from age 15 to 50 when adjusting for BMI and smoking at respective ages, educational level, and age at baseline in a multivariate random effects model. Longitudinal decreases in age were dependent on BMI, showing that relative weight at age 15 was important for level of non-occupational activity at age 15, but not later in life at ages 30 or 50 (Figure 9). Moreover, men obese at age 50 started out at the same non-occupational activity level as non-obese at age 15, but had lower levels at ages 30 and 50.

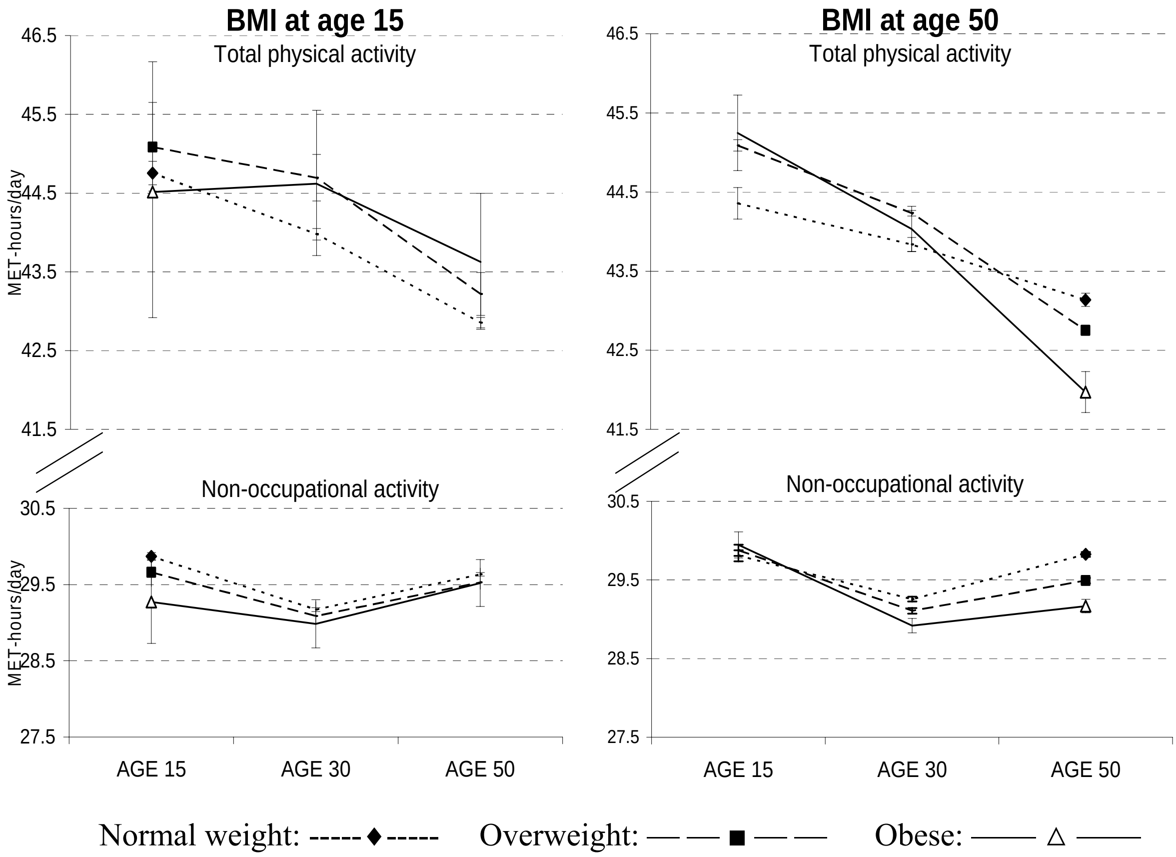


Figure 9 *Longitudinal changes in daily physical activity by age and BMI at age 15 and 50, estimated from random effects model, 95% CI indicated*

TEMPORAL TRENDS OF PHYSICAL ACTIVITY (PAPER III)

Total physical activity levels decreased over time since the 1930's in all age groups, as illustrated in Figure 10. These decreases over calendar time were also observed in a multivariate regression model, adjusting for BMI and smoking at respective age, and education, although they were slightly weaker (9% at age 15, 2% at age 30, and 3% at age 50, $p<0.001$).

Observed temporal trends for different activities at ages 15, 30 and 50 are shown in Figure 11. In multivariate analyses by age, when adjusting for BMI and smoking at respective age and education, work/occupational activity decreased at all ages ($p<0.001$). High intensity activities such as walking/bicycling and exercise decreased over time at all ages ($p<0.001$). Inactivity, i.e. low intensity activities (watching TV/reading), has been increasing among 15- and 30-year olds from 1960/70's after introduction of TV ($p<0.001$) and remained stable at a higher level among 50-year olds during 1970's to 1990's. Housework had been increasing among 30-year old men from the 1970's ($p<0.001$).

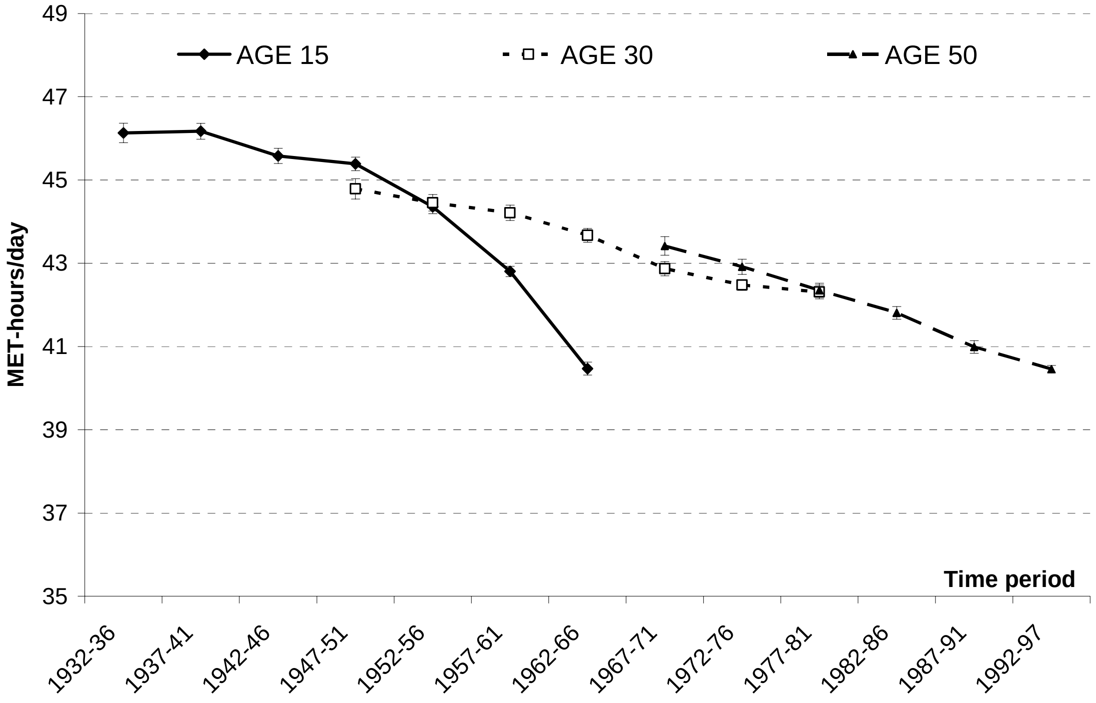


Figure 10 *Temporal trends of total daily physical activity by time period and age; 95% CI indicated*

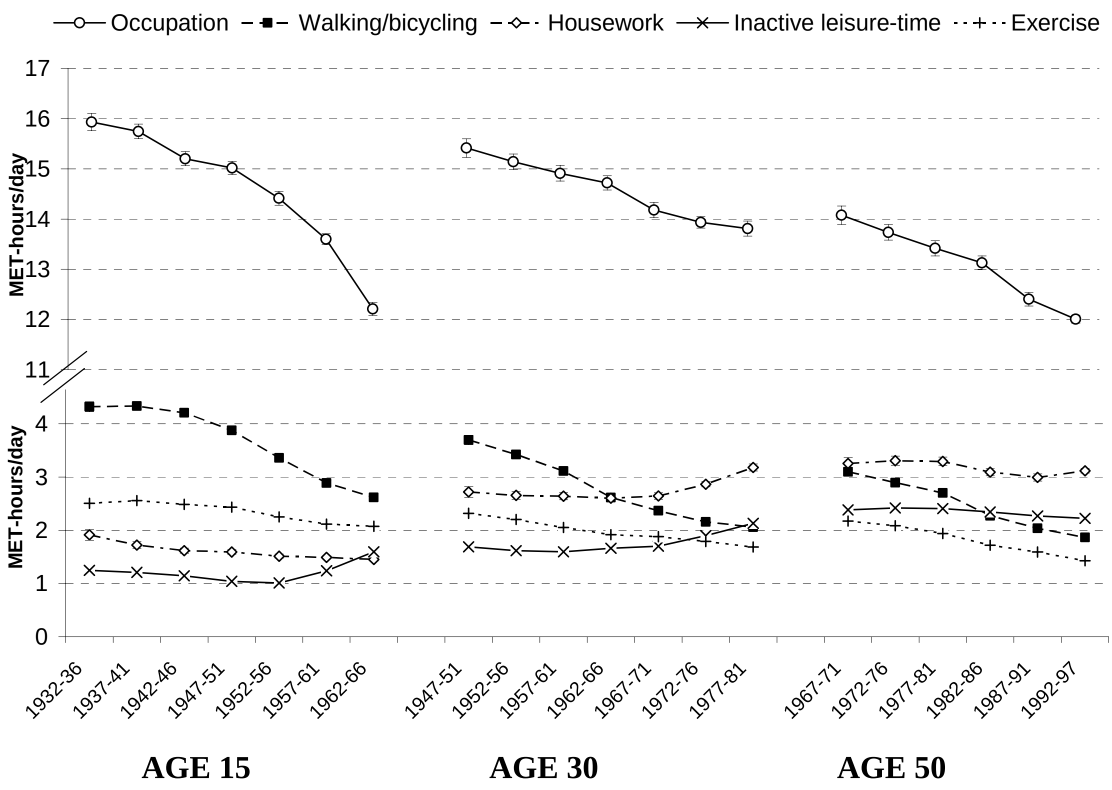


Figure 11 *Temporal trends of specific activities by time period and age; 95% CI indicated*

Occupational physical activity and prostate cancer risk (Paper IV)

During the nineteen years of follow-up, we observed 43,836, 28,702, and 19,670 cases of prostate cancer in the three cohorts of men who had classifiable jobs in 1960, classifiable jobs in 1970, and the same physical activity level in both 1960 and 1970 censuses, respectively. In 1960, 42% of men with classifiable jobs engaged in sedentary or light occupations, while in 1970, the corresponding proportion increased to 51%.

The relative risk for prostate cancer increased slightly with decreasing level of occupational physical activity in all three cohorts (p<0.001). The RR among men classified as holding sedentary jobs in both 1960 and 1970 was 11% higher than that in men classified as having the physically most demanding jobs in 1960 and 1970, as shown in Figure 12.

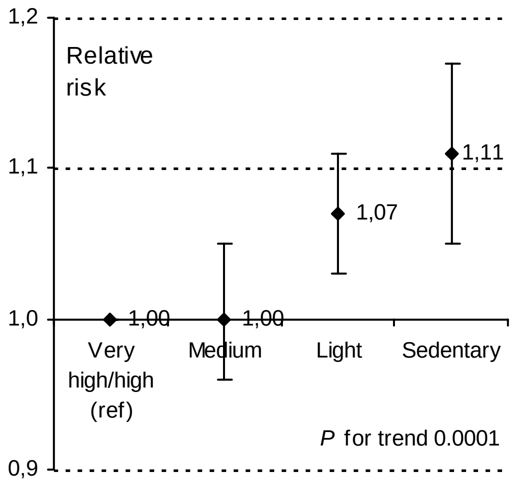


Figure 12 *Relative risk with 95 percent confidence interval for prostate cancer by the same occupational physical activity level in both 1960 and 1970. Relative risk adjusted for age by 5-year intervals, calendar year of follow-up by 5-year intervals, and place of residence*

Men who worked at sedentary jobs in 1960, but changed to more physically active jobs in 1970 were still at increased risk (sedentary in 1960 and very high/high in 1970, RR=1.07 95% CI 0.98-1.17) compared to men with a very high/high activity level in both 1960 and 1970.

Occupational activity and socio-economic status are based on the same variable (job title). Spearman correlation coefficient between occupational activity and socio-economic status was -0.67, -0.71 and -0.71 in the 1960 census, the 1970 census and in the cohort with the same level of physical activity in 1960 and 1970, respectively. Relative risk for prostate cancer among those being sedentary as compared to being very high/high active, with additional adjustment for socio-economic status was 1.09 (95% CI 1.00-1.18) in men with the same level of occupational activity in 1960 and 1970, but the model fit was not improved by adding socio-economic status. In the same model, the relative risk associated with socio-economic status was 1.06 (95% CI 1.00-1.13), when comparing senior and intermediate-level salaried employees to unskilled and semi-skilled workers. To further explore this, we performed stratified analyses of activity level and cancer risk by socio-economic status (Table 7). Since range of exposure of activity level was limited in some socio-economic groups, some exposure groups were collapsed and medium activity level was chosen as the reference group. Results within socio-economic strata were consistent with the inverse association between occupational physical activity and prostate cancer risk observed in the entire cohort (Table 7).

Table 7 *Relative risk (RR)[a] with 95 percent confidence interval (CI) for cancer of the prostate in the cohort of men with the same physical activity level in 1960 and 1970 stratified by socio-economic status. Results obtained by Poisson regression.*

	RR (95% CI)					
Occupational physical activity 1960 and 1970	Unskilled and semi-skilled workers [b]	Skilled workers [c]	Junior salaried employees [d]	Intermediate -level and senior salaried employees [e]	Farmers [b]	Entrepreneurs [f]
Very high/high	1.0 (0.9-1.0)	1.1 (1.0-1.2)	NA	NA	0.9 (0.5-1.6)	0.9 (0.8-1.2)
Medium	*1.0 Ref*	*1.0 Ref*	*1.0 Ref*	*1.0 Ref*	*1.0 Ref*	*1.0 Ref*
Light	1.2 (1.0-1.3)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-1.1)	NA	1.0 (0.8-1.2)
Sedentary	NA	1.3 (0.8-1.9)		1.1 (0.9-1.2)	NA	

a Relative risk adjusted for age by 5-year intervals, calendar year of follow-up by 5-year intervals, and place of residence

b Manual workers with less than two year of education after primary school. ”Farmers” distinguish from other by owning the property on which they work.

c Manual workers with at least two years of education after primary school

d Non-manual workers with maximum of two years of education after primary school; sedentary and light analyzed together due to insufficient number of observations in sedentary group

e Non-manual workers with more than two years of education after primary school

f More than two years of education after primary school. Distinguish from other by owning the property on which they work; sedentary and light analyzed together due to insufficient number of observations in sedentary group.

NA = not applicable

GENERAL DISCUSSION

Main findings

We have estimated the validity of self-administered *total* 24 hours physical activity levels as well as different types of activities in men and our questionnaire measures average long-term daily physical activity satisfactorily (Paper I). Deattenuated Spearman correlation between the questionnaire and the activity records (the reference method) was 0.56 (0.69 when adjusting for random error in the questionnaire) and the reproducibility coefficient was 0.65. Significantly higher validity correlations were observed in normal weight men (r=0.73) compared to overweight men (r=0.39).

In our large population-based cohort study of 33,466 men aged 45-79 years we found that total physical activity has been decreasing systematically with age in a cross-sectional setting (Paper II). The decrease with age was greater among obese men, current smokers, low educated men, and among men with poor or very poor self-rated health at the time of data collection. When following individuals from age 15 to 50 years retrospectively in the same cohort, total physical activity level decreased by two percent from age 15 to age 30 and four percent from age 15 to age 50 (Paper III).

Independently of age, we observed retrospectively temporal decreases of total physical activity by calendar-time during the last 60 years in the cohort of 33,466 men (Paper III). The decrease in total activity was nine percent among 15-year olds, two percent among 30-year olds and three percent among 50-year olds.

The data from our nationwide prospective cohort study supports the hypothesis that a low level of occupational physical activity might increase the relative risk of prostate cancer (Paper IV). Men with sedentary jobs both in 1960 and 1970 as well as in 1960 and in 1970 separately, had a small statistically significant excess relative risk compared to men who had very high or high levels of physical activity at work.

Methodology

This thesis is based on three different types of studies. The validity and reproducibility of a physical activity questionnaire was evaluated (Paper I) and used in a cross-sectional study of physical activity trends by age (Paper II) as well as retrospective longitudinal trends by age and over calendar-time (Paper III). In an observational study, we investigated the association between levels of occupational physical activity and prostate cancer risk in a cohort design (Paper IV).

PRECISION – ABSENCE OF RANDOM ERRORS

Random errors are errors that may give a deviation from the true value in an investigation, but would not give any deviation from the true value if the investigation was repeated an infinite number of times. Chance alone is an unlikely explanation to the observed associations in our large cohort study of 33,466 men in central Sweden (Paper II-III) and the nation-wide cohort based on the Swedish Censuses (Paper IV), since precision is improved with larger studies due to less variability in the estimate. The confidence intervals provide information about the precision of the investigation and test the statistical significance of the results observed to quantify the degree to which sampling variability may account for the results. We observed narrow confidence intervals, indicating high precision. However, chance findings can never be completely ruled out.

In our validation study (Paper I), we estimated the precision of the total physical activity measure by comparing repeated physical activity measures. The correlation was high between repeated measures, both for current physical activity and retrospectively at age 15, 30 and 50, indicating that random error is not a major problem for the activity instrument used in trend analyses (Paper II-III).

VALIDITY - ABSENCE OF SYSTEMATIC ERRORS

Bias may be defined as any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and risk of disease. There are two types of biases that may arise in epidemiologic studies; selection bias and information or observation bias. It is necessary to evaluate the role of bias as an alternative explanation for observed associations in interpreting study results.

Selection bias

Selection bias may be an issue in epidemiologic studies if the relation between exposure and outcome is different for those who participate and those who should be theoretically eligible for the study. In other words, selection bias refers to any error that arises in the process of identifying the study population.

In the validation study (Paper I), the participants might be more health conscious and more attentive in recalling and recording their activities than the general population, which may have lead to higher correlations in this group between the questionnaire and the physical activity records. However, we observed the same correlations in the subgroup of 68 men who participated in all four steps of the study as in the whole validation group. This observation suggests that a hypothetical selection due to health consciousness did not necessarily influence our estimates since the subgroup of 68 men might have been even more health conscious than the whole validation group. Moreover, characteristics of the validation group were comparable regarding BMI, smoking and total physical activity levels to the whole cohort where the physical activity measure was used for trend analyses.

In the analyses in a cross-sectional setting (Paper II), we included 33% of the eligible population. Our observed results of decreasing levels of total physical activity with age might be biased if our study population differs from the eligible population regarding the relation between the covariates of interest and the outcome physical activity. When comparing our study population with the general Swedish population, we observed the same rates of age, relative weight and education. Although we cannot compare levels of physical activity in the cohort with the Swedish population, the levels of physical activity in the cohort did not differ from levels in the validation study (Paper I). Our results of decreasing levels of activity with increasing age might be biased if, for instance, the participation rate in the cohort is lower among men with poor/very poor self-perceived health. Since the observed association was modified by self-perceived health, we would have underestimated the observed association of decreasing levels of physical activity with age if we unintentionally excluded men with poor/very poor health who were shown to have the greatest decrease with age among sub-groups of self-rated health.

If lower levels of physical activity at younger ages were associated with mortality, the observed time trends in Paper III could be overestimated, since we could only invite survivors to participate in the cohort. We could not include the theoretic retrospective population of 15, 30 and 50 year olds that would have been invited to participate in the study if they were still alive in 1997. To avoid potential selection bias, it would be more appropriate to do a longitudinal cohort study with several follow-up measurements. The disadvantage is that a longitudinal design requires very long follow-up. Moreover, when following the same subjects over time, we cannot compare the same age groups without comparing different subjects who might answer differently. However, our finding of decreasing levels of physical activity with age is consistent with other longitudinal studies assessing leisure-time activity (Barnekow-Bergkvist et al. 1996) (Anderssen et al. 1996), and the decreasing levels of total activity with time were expected.

In our analyses of occupational activity and prostate cancer risk (Paper IV), we could not include men without an occupation, since we could not classify job-activity level. The mortality of active workers is often lower than that of the population as a whole ("healthy-worker effect") (Rothman et al. 1998), indicating that relatively healthy people become or remain workers, whereas those who remain unemployed, retired, disabled, or otherwise out of the active worker population are as a group less healthy. However, in our 1960 data, a smaller proportion of cases compared to the whole study cohort had no occupational score, whereas in 1970, a larger proportion of cases had no occupational score compared to the whole study cohort, (since prostate cancer diagnosis is more common among older men and since older men were more likely to be retired in 1970 and not have a job code in 1970). But still relative risks of prostate cancer in relation to occupational activity were similar in 1960 and 1970, suggesting that any worker selection did not alter our risk estimates. We also excluded men with occupations that were not consistently classified into the same activity level by the three experts. However, this exclusion most likely did not affect the risk estimates, since this exclusion was probably regardless of either exposure or disease status.

Information bias

Information bias can occur whenever there are errors in the measurement of subjects, but the consequences are different, depending on whether the distribution for errors for one variable depends on the actual value of other variables. If the measurement error is systematic, the bias is referred to differential misclassification and the error may be in any direction. Random error is referred to non-differential misclassification and usually dilutes any observed risk estimate.

Misclassification of exposure

Information on occupational activity in Paper IV was assessed long before the diagnosis of prostate cancer, which rules out the possibility of differential misclassification of physical activity between cases and controls. A shortcoming is the indirect assessment of occupational physical activity on a group level, based on job titles. This proxy variable might only be a crude marker of the actual exposure level of individuals. However, when our physical activity matrix was validated against self-reported level of occupational physical activity in the 1970s, we found good agreement. Moreover, the use of job titles may even be an advantage, since the choice of vocation preceded the onset of the prostate cancer by many years, thus giving little room for reversed causation. Nonetheless, considerable non-differential misclassification of the factual physical activity, introduced by the crude job title classification, may have substantially attenuated the true dose-response (Rothman et al. 1998). The availability of repeated measures of occupational activity made it further possible to have a stable long-term measure of occupational activity. Changes in occupational activity levels between 1960 and 1970 or during follow-up time are unlikely to be related to prostate cancer status. Therefore they could lead to non-differential misclassification, but not bias the observed association.

However, information on total physical activity was not available in this study (Paper IV), and since we do not know the biological mechanisms by which physical activity might affect prostate cancer risk, the effect of lack of information about recreational physical activity may be of concern. If there is a systematic difference in recreational physical activity among men in different occupational activity categories, the dose-response association could be affected in an unpredictable direction. The observed association between physical activity and prostate cancer would be underestimated if men with sedentary jobs were more physically active during their leisure-time than men with strenuous occupations. Higher levels of leisure-time physical activity have been observed among higher educated men (Ruchlin et al. 1999) who usually have a more sedentary job. We did not, however, observe any differences in level of total non-occupational activity (including housework, transportation, miscellaneous activities besides leisure-time activity) between different educational groups (Paper II), which could serve as a proxy variable for different occupational activity levels.

Misclassification of outcome

The quantitatively estimated *total* daily activity in Paper II-III is based on our validated instrument that was shown to estimate total activity satisfactorily (Paper I). Although correlation coefficients were higher for energy expenditure (based on the individual's weight) compared to physical activity levels, the use of energy expenditure might reflect weight rather than actual physical activity levels. This is why we consider MET-hours as being independent of body weight a better measure of actual physical activity levels in our trend analyses (Paper II-III). The fact that older men (65-78 years) and heavy men (>26 kg/m^2) had lower validity correlations for total physical activity compared to younger men and lighter men, may have affected the results in the cross-sectional analyses (Paper II). The observed decreasing levels of total physical activity with age might actually be underestimated, since older men tended to overreport their total activity levels in the validation study.

When measuring *total* daily activity, it is important to estimate activities for 24 hours per day to be able to compare activity levels between subjects. Although we have intended to measure total physical activity, our results revealed that the questionnaire has not actually measured all domains of physical activity. Instead, we underestimated the total activity by about 20%, mainly due to common activities not asked for in the questionnaire, e.g. self-care/walking at home, sitting, and eating. Our assumption that missing activity time ("other") was due to common activities was confirmed in the activity records. Correcting the time reported in the questionnaire to 24 hours increased the strength of the linear relationship with the records considerably. However, this correction might lead to underestimation in men who have a higher mean intensity level than the assumed 2.0 MET during the time not reported and an overestimation in men with lower intensity level than 2.0 MET, and this may lead to a lower validity. Further, our correction might lead to an artificially narrower range of total activity level leading to lower observed validity correlation; or alternatively, a wider range leading to an artificially higher observed validity correlation (Delcourt et al. 1994). If this misclassification is covarying with age or the other covariates, it might have affected our results in an unpredictable direction.

The total activity level in our study was very similar to that estimated in a study of 206 eastern Finnish men, aged 50-60 years, (mean 42.5 MET-hours·d^{-1}, 95% CI: (40.0; 45.1) and 40.7 (38.6; 42.7) MET-hours·d^{-1} one year later), which is one of few studies measuring total 24 hours activity level with a questionnaire (Rauramaa et al. 1995). In a study of Greek men aged 30-82 years who were part of the

European Prospective Investigation into Cancer and Nutrition (EPIC) study, total mean 24 hours self-reported activity was 35.3 MET-hours/day when estimating occupational and leisure-time activities, household activities, walking, cycling, repairing, gardening and sleep (Trichopoulou et al. 2000). When adjusting the Stanford 7-day recall total activity to 24 hours in 28 American men aged 23-57 years, the observed total mean activity was 36.6 MET-hours/day (Richardson et al. 2001).

Accuracy of physical activity estimates may be influenced by individual variation in movement patterns and differences in the subjective way in which intensity of activities is reported, and also by the way that reported activity is converted to activity scores and energy expenditure. The published data on specific activity scores (MET) are merely averages, i.e. they do not take into account that some people perform activities more vigorously than others (Ainsworth et al. 1993; Ainsworth et al. 2000). Individual differences in energy expenditure for different activities can be large and the true energy expenditure for a person may or may not be close to the stated mean. When using MET values, we assume that the relation between energy expenditure and resting metabolic rate for a particular activity is the same for all individuals.

Moreover, using an assigned mean of different MET values to estimate a MET for a specific type of activity in the questionnaire, assumes that all individuals perform this type of activity at the same intensity level. However, there is a range of intensity levels for each type of activity, for instance exercise, since some men perform more vigorous activities such as running, while others lower intensity activities, such as bowling. This misclassification in the total activity score due to assigned average MET values is likely to be non-systematic and attenuate observed associations between total activity and other factors.

Information about physical activity at younger ages based on the same questions was available in the questionnaire, which enabled the study of longitudinal changes with age and over time in Paper III. The retrospective information is dependent on the participants' ability to remember daily activities at ages 15, 30 and 50. If older men recalling their activities at age 15, 30 and 50 for more distant time compared to younger men, would overestimate their reported activities at younger ages, the observed decrease of total activity over time would be overestimated due to differential misclassification by age. If, on the other hand, older men would underestimate their distant activities, our results would be underestimated. Difficulties in recalling could also be non-systematic, i.e. some men would overestimate and some men underestimate past physical activity, affecting both older and younger men, thus leading to non-differential misclassification. This random misclassification would typically attenuate observed associations (Rothman et al. 1998). Quality of recall of physical activity in the distant past was investigated in a study of 137 men and women who were initially interviewed in the 1960's and then reinterviewed in the 1990's (Falkner et al. 2001). There were no associations between BMI, marital status, or blood pressure and quality of recall of physical activity and although there were some differences in recalling physical activity by age ("good recallers" were younger, older men both over-, and under reported physical activity), and education ("good recallers" had more educational years), the authors concluded that the evidence did not support better recall by one group compared with the others. However, higher levels of current physical activity were observed among overestimators, and lower levels among "good recallers" (Falkner et al. 2001). Slattery and coworkers concluded that people can recall leisure-time activity patterns of several years ago with high reliability when comparing recalled data with original data 3-4 years earlier (Slattery et al. 1995). In contrast, older Swedish women systematically overreported their recalled leisure physical activity levels when compared to the original data 32 years earlier (Lissner et al. 2004). The authors claim that recall questionnaires for the distant past should be used with caution, particularly in older populations.

Misclassification of prostate cancer cases (Paper IV) in the Swedish cancer register is negligible; close to 100% of cases have been histopathologically verified. However, a distinct feature of prostate cancer is the high prevalence of latent carcinoma, found incidentally at autopsy or after surgical removal of prostate tissue. If the rate of false negatives is correlated with occupational activity level, this may affect the observed association. For instance, occupational activity level may be associated with socio-economic status and age. Regular visits to a physician in higher socio-economic groups and among older men may result in detecting latent prostate cancers among sedentary men (higher socio-economic group), leading to an overestimation of relative risk for the lower activity group or among older men. Although we did not observe any significant differences in relative risks between age groups (+/- 70 years) of having a sedentary job, nor in higher socio-economic groups compared to lower socio-economic groups, we cannot completely exclude a possible risk for misclassification of outcome.

Confounding

Confounding can be thought of as a mixing of the effect of the exposure under study on the disease with a third factor. This third factor must be associated with the exposure, and independent of that exposure, be a risk factor for the disease. All four studies in this thesis are based on either random sampling from the whole population (paper I) or the whole population (Papers II-IV), which is one way to control for confounding.

In the study based on a nation-wide population, we did not have any information for individuals on possible confounders (Paper IV). However, there are not many known strongly related risk factors for prostate cancer (Ross et al. 1996; Crawford 2003). Age is the strongest known risk factor for prostate cancer (Crawford 2003) and age is also associated with levels of physical activity (Papers II-III)(Trost et al. 2002), and was included in the multivariate model when studying occupational activity and prostate cancer risk. When adjusting for place of residence (as a proxy for differences in obesity and food habits) no major changes in relative risk estimates were observed. However, the small increased risk observed for prostate cancer in sedentary men might be explained by unknown and unmeasured confounding.

Both occupational activity and socio-economic status were independent risk factors for prostate cancer in our data (Paper IV). However, since they are both based on the same variable (job title) and thus correlated, it is difficult to clearly disentangle the effect of occupational activity from the effect of socio-economic status on prostate cancer. The relative risk estimates for physical activity were slightly attenuated when socio-economic status was included in the model, with no improvement in the model fit. A similar phenomenon was observed in a case-control study in Turkey, when socio-economic status also based on job title was included in the model of physical activity and prostate cancer risk (Dosemeci et al. 1993). Socio-economic status per se cannot be biologically associated with prostate cancer, but factors closely related to social status might be and this requires closer future investigating. However, in an earlier case-control study in Sweden, socio-economic status (based on occupational title) has not been associated with prostate cancer risk (Andersson et al. 1996). Moreover, the dose-response relation of occupational activity and prostate cancer risk was observed in all socio-economic groups in our data.

Generalizability

Given the population-based design, the external validity should be satisfactory and our results should be generalizable to the population, i.e. given a high internal validity without bias as discussed above.

Our validation study (Paper I) was population-based, and performed in a similar population as that where the questionnaire was being used (Paper II-III); men aged 45-79 years living in central Sweden, covering both the countryside and cities. The men in the validation study were not significantly different from the cohort participants, with regard to BMI, smoking or total physical activity level.

We showed that the population-based cohort used for trend analyses of physical activity (Paper II-III) well represents the Swedish population, since age composition and educational level was almost identical to the entire Swedish population of middle-aged and older men (Official Statistics of Sweden 1999) and since the prevalence of overweight in the cohort was similar as in the nationally representative sample from a survey of living conditions (Johansson et al. 1998). Moreover, our results are probably generalizable to most Western countries, since increasing prevalence of sedentary jobs, labor saving devices in the home and workplace, and motorized transports are not only a Swedish phenomenon.

Results from the nation-wide cohort of occupational activity and prostate cancer include *all* men in Sweden except men without an occupation, which makes these results generalizable to Swedish working men.

Interpretations and implications

VALIDITY OF TOTAL PHYSICAL ACTIVITY

The validity and reproducibility of the measure of total physical activity used in trend analyses was evaluated and it was shown to measure average long-term total daily activity satisfactorily. The record is not a perfect reference method for assessing daily activity, and a combination with a more objective measurement approach would have provided even stronger validation methodology. However, the record made it possible to evaluate the validity of different types of activities that were the base for the total activity score in the questionnaire and seven-day activity records have been shown to be a good estimate of total energy expenditure when compared to doubly labeled water (Conway et al. 2002). Moreover, some other reference methods, such as doubly labeled water or accelerometer would probably – apart from being much more costly and lengthy – have lowered the response rate.

To our knowledge, there are only three relatively comparable validation studies to ours. They show similar validity and reproducibility correlations when comparing their questionnaires – aiming at measurement of total 24 hours energy expenditure in kcal (Arroll et al. 1991; Pols et al. 1997) or MET-hours (Richardson et al. 2001) – to activity records. In the Stanford 7-day recall questionnaire, work and leisure-time activities as well as sleep were recalled in 28 men and then sedentary activities were estimated by subtracting the time in activities and sleep from 24 hours (Richardson et al. 2001). The recalled mean 24-hour physical activity was 36.6 MET-hours/day and the mean total activity based on activity records was 39.8 MET-hours/day. These results are similar to estimates in our activity records (39.0 MET-hours/day). The validity correlation between 7-day recall and records was 0.58 and the reproducibility correlation coefficient was 0.60 (Richardson et al. 2001). When comparing estimated energy expenditure based on a 28-item questionnaire with 4x3-day activity records in 64 men, Spearman correlation coefficient was 0.66; reproducibility 0.76 (Pols et al. 1997). In the third study, not directly comparable to our study due to the short-term period covered by the questionnaire, Spearman correlation for total energy expenditure was 0.91 when comparing a 3-month recall questionnaire with one 7-day activity diary, both based on the same four activity categories (Arroll et al. 1991).

An international physical activity questionnaire (IPAC) was developed by an International Consensus group for facilitating international comparisons of physical activity (Craig et al. 2003). The short version of the questionnaire (9 items) provided information on walking, vigorous-moderate- and sedentary activity and the long version (31 items) collected detailed information on household and yard work, occupational activity, transport, leisure-time activity and sedentary activity. When comparing the self-reported total activities in MET-min/wk against accelerometer data, the validity correlation was around 0.30 in the 12 countries participating in the study and the reproducibility coefficient was around 0.80 when repeating the IPAC after one week (Craig et al. 2003).

Most of the other existing questionnaires measure only some types of activities. A simultaneous evaluation of 10 commonly used physical activity questionnaires against treadmill exercise performance, vital capacity, body fatness, 4-week physical activity histories, and accelerometer readings revealed that the validity estimates largely depended on the choice of reference method (Jacobs et al. 1993). Performance of heavy intensity physical activities was related to treadmill performance and body fat; fewer questionnaires related to any reference method with regard to light or moderate activity. Four-week activity history was on average best correlated with the questionnaires although the validity coefficients ranged between -0.16 and 0.74 (Jacobs et al. 1993). The authors noted that "the capacity of a questionnaire to perform well against validation measures does not appear to be solely related to its length or attention to detail. More important seems to be the logic with which its questions are constructed" (Jacobs et al. 1993).

Differences in self-reported physical activity between subgroups defined by body weight have been evaluated in two other studies (Buchowski et al. 1999; Timperio et al. 2003). Physical activity recalls compared to accelerometer readings were not different in overweight compared to normal weight men in a study of young men (mean age of 38 years) (Timperio et al. 2003). This is in contrast to our results in older men (mean age of 63 years) where overweight men had lower validity coefficients of self-reported physical activity compared to normal weight men. Our results are indirectly in agreement with another study showing that men with increasing percent body fat significantly overestimated duration of more strenuous activities ($\geq$4.5 METs), while underestimating moderate activities (2.5-4.4 METs) when comparing self-reported activity with indirect calorimetry (Buchowski et al. 1999).

AGE AND LIFESTYLE FACTORS IN RELATION TO PHYSICAL ACTIVITY

Age

The decline in physical activity with age may be the most consistent finding in descriptive epidemiology of physical activity. Our observation of decreasing physical activity levels with age are in concordance with several other studies assessing leisure-time physical activity or exercise in different populations (Lee et al. 1992a; Hays et al. 1999; Booth et al. 2000; Caspersen et al. 2000; Trost et al. 2002). Although the phenomenon is well documented and well accepted, it is not well understood. For example, it is not known whether the mechanism of the decline is primarily environmental or biological. There is evidence of a physical activity decline with age also in animal studies, supporting an interpretation that the decline is at least partly a biological phenomenon (Ingram 2000).

In contrast to other studies, we estimated levels of changes of *total 24 hours* physical activity with age. The decrease of four percent in total activity from age 15 to 50 as well as from age 45-49 to 75-79 in the multivariate models corresponds to 1.8 MET-hours per day. This corresponds to an approximate expenditure of 130 kcal per day in a man weighing 75 kg. Furthermore it may be translated into about *30 minutes of daily walking* at a moderate pace (Ainsworth et al. 1993). Surprisingly, our estimates of decrease in daily physical activity with age correspond to the public health recommendations of minimum levels of physical activity per day (Pate et al. 1995).

Our results of a decline in physical activity from age 15 to age 30 was mostly attributed to non-occupational activity and not to occupational activity and the teen years have been identified in other studies as an age of great decline in leisure-time activity (Caspersen et al. 2000; Sallis 2000). A decrease in leisure-time physical activity from age 15 to age 30 has been observed both in longitudinal studies where moderate to heavy activities decreased and light activities and inactivities increased (Anderssen et al. 1996; Barnekow-Bergkvist et al. 1996; Telama et al. 2000), as well as in a cross-sectional study where the proportion of exercisers decreased with age (Raitakari et al. 1996).

In the cross-sectional analyses, we observed that the decline in total physical activity was greatest among the oldest ages, and this was also observed in a cohort of the US Harvard alumni who were followed for 20 years, who decreased their leisure-time energy expenditure after the age of 70 (Lee et al. 1992a). Both leisure-time physical activity as well as occupational activity declined with age (age 20 years to 60+) in a cross-sectional setting of Australian adults (Salmon et al. 2000).

Education

A positive association has been observed between higher level of education with higher levels of leisure-time activity (Caspersen et al. 1986; Salmon et al. 2000). In contrast, we observed an inverse association between education and total levels of physical activity. This was not surprising since lower education is associated with higher levels of occupational physical activity. However, we did not observe any association between non-occupational activity and educational level, and this may be due to that we included all activities/inactivities outside of work, not only exercise/leisure-time.

Body mass

Our results further support previous studies reporting an inverse association between leisure-time physical activity and obesity (Coakley et al. 1998; Martinez-Gonzalez et al. 1999). The association between high body mass index and lower levels of total physical activity found in our data was expected, since the total physical activity levels are associated with the total energy expenditure. Obese men had 2.6% lower activity levels compared to normal weight men, which corresponds to an average of 1.1 MET-hour lower activity level per day or *20 minutes of walking* at a moderate pace (Ainsworth et al. 2000). In a review of prospective studies of weight gain, leisure-time physical activity at follow-up was consistently inversely associated with weight gain, whereas results were inconsistent when estimating physical activity at baseline (Fogelholm et al. 2000).

TIME TRENDS OF PHYSICAL ACTIVITY

To our knowledge, there are no previous studies evaluating trends in total physical activity levels, therefore we cannot compare our results showing decreasing trends of total activity over calendar-time to other studies. Temporal trends of leisure-time physical activity and exercise show increasing levels in Sweden (Johansson et al. 1998; Statistics Sweden 1999), the U.S. (Jacobs et al. 1991) and Canada (Craig et al. 2004) but are difficult to compare to our findings of decreasing levels of exercise, due to different age groups and different definitions and measures of exercise. Six national Canadian surveys between 1981 and 2000 were compared according to a "sufficient activity" for health of +3 MET-hours/day (corresponding to about one hour of daily walking) and prevalence of activity increased during the 20 years from 20% to 40% (Craig et al. 2004). When estimating recommended levels of physical activity, defined as moderate-intensity physical activity ≥5 times per week for 30 minutes at each time or more, results indicated that leisure-time physical activity trends in the U.S. during the 1990's have remained unchanged (Centers for Disease Control and Prevention 2001). We were not able to estimate time trends of the recommended activity levels due to the design of our questionnaire. Prevalence of participation in any leisure-time activitiy has been shown to increase among Swedish 16-year old boys from 68% in 1974 to 74% in 1995 (Westerstahl et al. 2003). We observed decreasing levels of exercise among 15-year olds during the 1930's to the 1960's.

A possible explanation for the contradictory results of decreasing levels of leisure-time activities over time in our data may be that concepts about exercise and leisure-time activities have changed over time. For example, some low or moderate intensity physical activities such as walking and gardening may not have been perceived as "exercise" twenty years ago, whereas today they are, and this may partly explain observed increasing levels of exercise in many studies. We estimated levels of physical activity for time trend analyses retrospectively at one occasion in 1997, which possibly eliminated differences in definition of exercise over time. When Lee and coworkers estimated different intensity levels of leisure-time activity, they actually observed a decline in vigorous sports during a twenty-year period in American men and an increase in light and moderate sports (Lee et al. 1992a) and similar results were observed by Jacobs and coworkers (Jacobs et al. 1991). Moreover, due to increasing health consciousness, there may be a trend for individuals to over-report physical activity levels.

The decreasing levels of total physical activity over time may explain some portion of increasing incidence rates of chronic diseases associated with physical activity. Prevalence of obesity has increased rapidly in the U.S. since the 1970's (Flegal et al. 1998) and in Sweden since the early 1980's (Lissner et al. 2000), and the problem of obesity is becoming apparent worldwide, both among adults, children and adolescents (IARC 2002). In our data, observed total daily activity level decreased on average by 3.0 MET-hours for 50-year olds between the 1960/70's and 1990's, corresponding to about *45 minutes* of daily brisk walking or gardening or *half an hour* of playing tennis or *20 minutes* of running (Ainsworth et al. 1993). It also corresponds to having a full-time job where, instead of sitting half of the time, you are mostly standing up. On average, the annual decrease was 0.1 MET-hours each year during this 30-year period, corresponding to a theoretical weight gain of about 0.3 kg in one year or 9 kg in 30 years in a 75-kg man. This can be calculated since 0.1 MET-hours/day equals to about 7.5 kcal per day in a 75-kg man (0.1 MET-hours × 75kg) and assuming that 1 kg of fat tissue corresponds to about 8000 kcal (McArdle et al. 2001). Therefore, a decrease in 7.5 kcal of energy expenditure per day with a constant energy intake would theoretically result in a weight gain of about 0.3 kg in one year in a 75-kg man ((7.5 kcal/day × 365 days) / 8000 kcal/kg).

PHYSICAL ACTIVITY AND PROSTATE CANCER RISK

Results from our investigation support an inverse association between occupational physical activity and prostate cancer. Although the observed risk represents a weak association (11% increased risk among sedentary workers), it does not rule out a causal connection. The implications for public health could be large, since prostate cancer is the third most common cancer among men worldwide and the most common cancer in Swedish men with incidence rates still increasing in parallel with decreasing physical activity levels.

The exposure information on occupational physical activity was assessed long before the onset of prostate cancer. This fact makes the risk for reversed causation rather improbable, which is necessary for considering a causal relation. Moreover, people do not change job categories that often, which in most cases, leads to a stable lifelong measure of occupational physical activity in our data. We observed a statistically significant dose-response relation between decreasing level of occupational activity and prostate cancer risk, which may further support a causal relation.

Biologic plausibility

Physical activity has effects on multiple biologic systems and many mechanistic pathways are possible. The association between prostate cancer and physical activity may be explained biologically by at least three different possible mechanisms. Physical activity may decrease the risk of prostate cancer (a) by decreasing testosterone levels (Strüder et al. 1998) and increasing levels of sex hormone-binding globulin (SHBG) (Zmuda et al. 1996), (b) by decreasing levels of insulin-like growth factor I (IGF-I) (Eliakim et al. 1998; Yu et al. 2000), and (c) by enhancing the immune system (Shephard et al. 1995). Moreover, physical activity might be associated with lower prostate cancer risk through its role in controlling body weight (Crawford 2003).

Previous studies

The association between physical activity and prostate cancer risk has been studied in at least 34 cohorts and case-control studies with conflicting results (Table 8). Among these 34 publications there were some multiple publications from the same study. From the prospective cohort of Harvard Alumni Health Study, which is an ongoing study of men who were undergraduates at Harvard University between 1916 and 1950, we have only included the latest updated study of physical activity and prostate cancer (Lee et al. 2001a) in Table 8. We excluded the following updates: (Lee et al. 1992b; Lee et al. 1994) but included the study by Paffenbarger (Paffenbarger et al. 1987), since it also includes analyses of longshoremen. Likewise, we excluded the two first studies from the cohort study of National Health and Nutrition and Examination I Survey (Albanes et al. 1989; Steenland et al. 1995) and only included the latest update by Clarke (Clarke et al. 2000).

Table 8 *An overview of results from 30 published studies on occupational physical activity (OPA) and/or leisure-time physical activity (LTPA) in relation to prostate cancer risk in men (results from a study can be included in more than one activity category)*

Main results	**Number of studies References (number of cases)**					
	Cohort studies			**Case-control studies**		
	Occupational physical activity	Leisure-time physical activity	Combined OPA and LTPA	Occupational physical activity	Leisure-time physical activity	Comb. OPA and LTPA
Inverse association statistically significant	**4** *Norman 2002 (43836)* Clarke 2000 (201) Hsing 1994 (264) *Vena 1987 (8116)*	**3** Wannamethe 2001 (120) Oliveria 1996 (94) Hartman 1998 (317)	**3** Clarke 2000 (201) Hartman 1998 (317) Thune 1994 (220)	**4** *Bairati 2000 (64)* *Villeneuve 1999 (1623)* Dosemeci 1993 (27) Brownson 1991 (2878)		
Inverse association not significant	**3** Hartman 1998 (317) Thune 1994 (220) *Paffenbarger 1987 (30)*	**2** LundNilsen 2000 (644) Severson 1989 (206)	**1** Will 1999 (2523)		**2** *Andersson 1995 (256)* Yu 1988 (1162)	
No association	**3** LundNilsen 2000 (644) *Putnam 2000 (101)* Severson 1989 (206)	**7** *Lee 2001 (439)* *Putnam 2000 (101)* *Pukkala 2000 (69)* Clarke 2000 (201) Liu 2000 (982) Giovannucci 1998a (1362) Thune 1994 (220)	**1** Severson 1989 (206)	**1** *Whittemore 1995 (1665)*	**3** *Whittemore 1995(1665)* Bairati 2000 (64) *Villeneuve 1999 (1623)*	**1** *Villen-euve 1999 (1623)*
Positive association statistically significant		**2** Cerhan 1997 (71) *Polednak 1976 (?)*		**3** *Lacey 2001 (243)* Ilic 1996 (101) *Lemarchand 1991 (452)*	**1** Sung 1999 (90)	
Positive association not significant					**2** *Lacey 2001 (243)* West 1991 (358)	

Assessment of *lifetime activity* or activity for a specific *time period in the past* is indicated with *italic font*

Occupational physical activity

In comparison to our data, nine other cohort studies evaluated the association between occupational physical activity and prostate cancer risk (Table 8), but only three studies besides ours found a statistically significant inverse association, ranging between 10% to 70% increased risk among sedentary workers (Vena et al. 1987; Hsing et al. 1994; Clarke et al. 2000). Vena and coworkers studied prostate cancer mortality and collected job titles from death records in 430,000 men in Washington State and coded them into levels of activity which is comparable to our assessment of exposure in paper IV (Vena et al. 1987). Proportionate mortality rates for prostate cancer for men with a low job-activity level and a high activity level, were 109 ($p<0.05$) and 93 ($p<0.05$) respectively. In Shanghai, occupational information of the urban population was obtained from a national census and coded into activity levels; additional information on occupation was collected via interviews for prostate cancer cases which were identified through the Shanghai Cancer Registry (at the time of the diagnosis) (Hsing et al. 1994). The standardized incidence ratio (SIR) for having an inactive job was 1.2 (95%CI 1.0-1.05). In the National Health and Nutrition Examination Survey I (NHANES I), occupational physical activity was self-reported among 5,300 men and the relative risk for being inactive as compared to being very active was 1.7 (95%CI 1.1-2.7) (Clarke et al. 2000).

Non-significant inverse associations between occupational activity and prostate cancer risk were observed in five studies while there were no associations in three studies (Table 8). Our study is the largest study performed to date, thus it has enough power to show even weak associations to be statistically significant, which may be one explanation for our finding of a small, but statistically significant increased risk in sedentary men. Four out of eight case-control studies showed a statistically significant inverse association between occupational activity and prostate cancer risk and three showed statistically significant positive associations (Table 8).

Leisure-time activity

For leisure-time physical activity, significant inverse associations ranging from 30% to 60% are observed in some cohort studies (Oliveria et al. 1996; Hartman et al. 1998; Wannamethee et al. 2001), non-significant inverse associations in a few (Severson et al. 1989; Lund Nilsen et al. 2000), but many cohort studies did not observe any association (Table 8). Two cohort studies showed a significant positive association (Polednak 1976; Cerhan et al. 1997). In the Health Professionals Follow-up Study, an inverse association with recreational physical activity was observed in a subgroup of metastatic prostate cancer only (200 cases), not for all prostate cancers (Giovannucci et al. 1998a). Results for recreational activity in case-control studies were not significant in any of the published studies (Yu et al. 1988; West et al. 1991; Andersson et al. 1995; Whittemore et al. 1995; Villeneuve et al. 1999; Bairati et al. 2000; Lacey et al. 2001), except for one study in a Taiwanese population showing a positive association (Sung et al. 1999).

Physical activity assessment

The methods used in previous studies of physical activity and prostate cancer risk were heterogeneous which makes it difficult to compare results. No clear pattern of risk decreases or increases by type of activity was found in published studies. Physical activity has been assessed, as well as combined and presented, in different ways. In most studies, physical activity levels were assessed by a questionnaire or an interview whereas in some studies occupational activity was assessed by collecting job titles from national records. In some studies recreational activity included sports only (Polednak 1976) and in others different recreational activities such as walking, biking, sporting, gardening, etc was combined (Wannamethee et al. 2001). The mode of activity also differs, from one question about level of activity (low, medium, high) (Thune et al. 1994; Clarke et al. 2000) to more detailed information about frequency, intensity/type, duration (Giovannucci et al. 1998a; Lee et al. 2001a). In Finland, cancer rates in world class athletes were compared with national cancer rates (Pukkala et al. 2000). Perhaps the assessment of occupational activity is more homogenous compared to recreational activity and there seem to be more homogenous results for this type of activity; a majority of studies show an inverse association between occupational physical activity and prostate cancer risk (Table 8).

When combining recreational and occupational activity, three studies of five find an even stronger risk reduction (Thune et al. 1994; Hartman et al. 1998; Clarke et al. 2000). These results are of interest since they suggest that total activity may be more relevant in etiological studies than one type of activity alone. Severson and colleagues estimated total 24-hour activity as time spent in five different activity levels including sleep in Japanese men living in Hawaii, but no association was observed between physical activity level and prostate cancer risk (Severson et al. 1989).

In the context, a large number of studies have been conducted on physical activity and different cancer sites and there seems to be convincing evidence that physical activity reduces the risk of colon cancer and possibly breast cancer (Friedenreich et al. 2002; IARC 2002). These results show that the physical activity instruments used have the capability to detect an association between physical activity and cancer, although the association may have to be quite strong. There may also be an association between physical activity and cancer of the prostate, endometrium and lung, but there are an insufficient number of studies to draw conclusions about other cancer sites (Friedenreich et al. 2002).

Life-time physical activity

Seven cohort studies and five case-control studies estimated life-time physical activity or physical activity during specific time periods in the past, indicated with *italic font* in Table 8. There do not seem to be any clear patterns of consistent increases or decreases in risk in the studies that assessed current activity only or in the studies that assessed lifetime activity or activity for a specific time period in life. This lack of consistency may be due to different assessment methods used and different time windows measured. Two case-control studies estimated physical activity levels during puberty (Andersson et al. 1995; Villeneuve et al. 1999), a period in life which may be of importance for prostate cancer initiation since prostate cancer is a hormone-related disease. In Canada, strenuous occupational activities in the mid-teens or early twenties appeared protective against prostate cancer (Villeneuve et al. 1999). However, no association was observed for leisure-time activity at young age in this study. In a Swedish case-control study, leisure-time physical activity during puberty was inversely associated, although not statistically significant, with prostate cancer risk (Andersson et al. 1995). These results indicate that physical activity early in life might be of importance for prostate cancer risk.

Risk assessment in subgroups

An association between physical activity and prostate cancer risk may be modified by other risk factors and some studies report results from sub-group analyses. Younger men seemed to be at lower risk in relation to activity level compared to older men in some studies (Le Marchand et al. 1991; Oliveria et al. 1996; Liu et al. 2000; Lee et al. 2001a), but in contrast, there is a larger risk reduction in older men in other studies (Thune et al. 1994; Giovannucci et al. 1998a) while there does not seem to be any difference in risk between age groups in others (Lee et al. 1994; Norman et al. 2002).

Few studies have evaluated differences in physical activity level and prostate cancer risk between ethnic groups. A greater increase in risk among sedentary African-Americans compared to sedentary whites was observed in all three studies (Yu et al. 1988; Whittemore et al. 1995; Clarke et al. 2000).

Dose-response relation

The potential dose-response relation was examined in 24 studies. A statistically significant trend (Brownson et al. 1991; Dosemeci et al. 1993; Thune et al. 1994; Hartman et al. 1998; Bairati et al. 2000; Clarke et al. 2000; Norman et al. 2002) or a borderline significant trend (Hsing et al. 1994; Wannamethee et al. 2001) of increasing risk of prostate cancer with lower levels of physical activity was observed in 9 studies, but two studies found a trend of increasing risk with increasing activity (Le Marchand et al. 1991; Cerhan et al. 1997). Thirteen studies did not observe any trend (Paffenbarger et al. 1987; Severson et al. 1989; Andersson et al. 1995; Whittemore et al. 1995; Oliveria et al. 1996; Giovannucci et al. 1998a; Will et al. 1999; Villeneuve et al. 1999; Liu et al. 2000; Lund Nilsen et al. 2000; Putnam et al. 2000; Lacey et al. 2001; Lee et al. 2001a).

Public health issues

In Paper III, we observed decreasing trends in physical activity levels over calendar-time, both occupational and non-occupational (Paper III). For 50-year olds, we were able to measure physical activity trends since the 1960's, the same period in time when we first measured occupational physical activity in the prostate cancer study, and levels of both occupational and non-occupational activity have decreased ever since. If the inverse association between physical activity and prostate cancer observed in our study is true, these negative trends in physical activity in Sweden could have implications for prostate cancer among older men which may partly explain the observed increasing incidence rates of prostate cancer. We also observed decreasing levels of physical activity with age, which is the strongest known risk factor for prostate cancer to date. Thus prostate cancer risk increasing with age might partly be mediated through mechanisms related to decreasing levels of physical activity with age.

The physical activity recommendation from the Centers of Disease Control and Prevention and the American College of Sports Medicine, emphasizes the importance of the total amount of activity performed rather than the specific manner in which it is performed (Pate et al. 1995). We have estimated total daily physical activity with a validated questionnaire, and showed decreasing trends of physical activity levels with age and over time, during the last 60 years. This probably has great public health implications for chronic diseases that are associated with physical activity and might explain a large portion of the rapid increase in overweight and obesity and several other chronic diseases observed during the last decades. Physical activity may be associated with prostate cancer risk and the increasing incidence rate of prostate cancer might partly (if the association is causal) be explained by the negative trends over time of physical activity levels. From a public health point of view, it is of greatest importance that we break this negative trend of decreasing total physical activity levels with age and over time. It is rather impossible to change trends in occupational activity levels, but increased non-occupational activity could be encouraged by adapting the infrastructure to facilitate the practice of regular common activities such as walking and bicycling.

FUTURE RESEARCH

The fact that physical activity is associated with health has been known for a long time, but many areas still need to be further explored, for instance, its relation to cancer. Physical activity as a factor related to prostate cancer has been investigated previously with inconsistent results. There are some methodological considerations needed to be taken into account in future studies when exploring the role of physical activity and prostate cancer risk. In most studies, the physical activity measure has been derived from a questionnaire, which is the only suitable method in large-scale epidemiological studies, measuring occupational activity and/or leisure-time activity. However, it is important to investigate *different types of physical activities* (leisure-time, occupational, transportation, household) as well as the *frequency, duration and intensity*, since we do not know if it is the average total physical activity or the shorter periods of very intensive activity influencing sex hormones levels that are of importance. When designing a physical activity questionnaire, it would also be of great interest to be able to estimate levels of physical activity according to the public health recommendations of a minimum of 30 minutes per day of moderate intensity activities (Pate et al. 1995). Even more important may be the need for international consensus on physical activity questionnaires and categorization of activity levels, for easier comparison between studies.

Another important aspect is to look at *lifetime physical activity*, including changes in activity levels. This is most often not covered by one single measure as often used in cohort studies. There may be a long latency between cancer and its etiologic factors. There could be a specific period in life that is important for future prostate cancer development, for instance, in adolescence, when influence of physical activity on hormone levels might be stronger than in adult life.

Moreover, it is important to use *validated instruments*, since the need of high validity and precision of the instrument used is indispensable for finding an association especially if the association is weak. A combination of different reference methods (objective and subjective) when designing the validity study may provide a stronger validation methodology.

Epidemiological studies should be designed to allow full consideration of *confounding* and *effect modification*. In our study, we could not clearly disentangle the association of occupational physical activity from socio-economic status regarding prostate cancer risk. This has also been the case in other studies of occupational activity adjusting for socio-economic status (Dosemeci et al. 1993). Therefore, future studies should include specific information on physical activity both at work and during leisure-time, as well as detailed information on income, education, and training to make it possible to better classify subjects into socio-economic groups. Perhaps, even more important is to study if any observed association between physical activity and prostate cancer is modified by another risk factor, for instance, age, body weight, or family history, why large studies are needed to have enough statistical power to perform such analyses.

Furthermore, experimental studies of physical activity and *"intermediate" endpoints*, such as sex hormone levels and prostate specific antigens (PSA), could increase the understanding of physical activity and prostate cancer risk. The *biological mechanisms* for physical activity and prostate cancer risk most often discussed are through hormones. Although associations between high levels of testosterone and IGF-I and prostate cancer have been observed, further investigations are needed to explain in more detail the relation between high levels of physical activity and levels of testosterone and IGF-I, which is not completely understood. More studies are needed to clearly understand these relations if they exist.

It would be preferable in future studies to investigate trends of different types of physical activity as well as total activity with age and over time *prospectively*, among both men and women. Physical activity measures would probably be more valid if participants were followed over time, instead of collecting data retrospectively. Moreover, it would be of interest to investigate associations of different types of physical activity as well as total activity with other lifestyle factors, including diet. How to *implement recommendations* of physical activity in the leisure-time, as well as in schools and at work places is an indisputably important challenge for the future.

CONCLUSIONS

- Total present daily physical activity can be estimated satisfactorily using our simple self-administered questionnaire

- Total daily physical activity decreases with age, both in cross-sectional and longitudinal settings

- Total daily physical activity has been systematically decreasing during the last 60 years

- Sedentary and light activity occupations may slightly increase the relative risk for prostate cancer – the third most common cancer worldwide and the most common cancer among Swedish men with an increasing incidence rate since the 1960's.

- A decrease in physical activity during the last decades is paralleled by an increase in prevalence and incidence of some chronic diseases, especially obesity

- Effective preventive strategies should be undertaken to switch the negative trends in total physical activity levels in the Swedish population

SAMMANFATTNING (SUMMARY IN SWEDISH)

Fysisk aktivitet minskar risken för flera kroniska sjukdomar och kan ge en ökad livslängd. Inaktivitet har associerats med vissa cancerformer men trots att ett samband mellan fysisk aktivitet och till exempel prostatacancer – den vanligaste cancerformen bland svenska män – är biologiskt möjlig, visar publicerade studier olika resultat. En anledning skulle kunna vara att de vanligast förekommande frågeformulären endast mäter motionsvanor och/eller fysisk aktivitet under arbetstid, vilket kan leda till felklassificering och underskattning av de de uppmätta riskestimaten. Flera av de kroniska sjukdomar som associerats med inaktivitet ökar både över tid och med ålder, men trots ett stort folkhälsointresse för fysisk aktivitet har endast ett fåtal publicerade rapporter studerat ålders- och tidstrender för olika typer av fysisk aktivitet och/eller den totala aktiviteten.

Vi utvärderade validiteten och reproducerbarheten för ett kort självadministrerat frågeformulär som avser mäta total fysisk aktivitet över dygnet. Formuläret innehåller frågor om fysisk aktivitet på arbetet, spenderad tid för gång/cykling, hem/hushållsarbete, motion och inaktiv fritid, samt sömn. Den totala fysiska aktiviteten uppskattades kvantitativt genom att slå samman aktiviteterna och mättes som MET-timmar per dygn (metabola ekvivalenter av inaktivitet). Etthundraelva män från Uppsala län deltog i studien. De fyllde i hela frågeformuläret samt registrerade en eller två aktivitetsdagböcker, vilka användes som referensmetod. Spearmans korrelationskoefficient uppmättes mellan total fysisk aktivitet baserad på frågeformuläret jämfört med aktivitetsdagboken till 0.56 (validitet) (r=0.69 justerat för slumpmässigt fel i frågeformuläret) och mellan det första och andra upprepade frågeformuläret till 0.65 (reproducerbarhet). Frågeformuläret kan därmed betraktas som ett instrument som mäter total fysisk aktivitet relativt väl.

Total fysisk aktivitet och olika typer av aktiviteter studerades i relation till 1) ålder i en tvärsnittsstudie, 2) ålder i en longitudinell miljö, 3) samt tid. Med det validerade frågeformuläret samlade vi information om nuvarande fysisk aktivitet, samt fysisk aktivitet retrospektivt i åldrarna 15, 30, och 50 år, i en populationsbaserad kohort med 33466 män i åldrarna 45-79 år. Total fysisk aktivitet minskade med ålder, både i tvärsnittsstudien (-4% från 45-79 år) och i de longitudinella analyserna (-4% från 15-50 år). Minskningen var störst bland feta män, nuvarande rökare, lågutbildade män, samt män som skattade sin hälsa lågt (dålig eller väldigt dålig). Total fysisk aktivitet minskade över en 60-årsperiod i alla åldersgrupper (15, 30, respektive 50 år).

Effekter av fysisk aktivitet på arbete och risken att utveckla prostatacancer undersöktes i en nationell kohort (cancer-miljöregistret): svenska folk- och bostadsräkningar från 1960 och 1970 kopplades med uppgifter från cancerregistret under perioden 1971-1989. Nivåer av fysisk aktivitet baserades på klassningar av yrkeskoder i folk- och bostadsräkningarna. Totalt förekom 19670 prostatacancerfall under en uppföljningsperiod på 19 år bland män som hade samma nivå av fysisk aktivitet på arbetet både 1960 och 1970 (n=673443). Stillasittande män löpte en liten, men statistiskt signifikant ökad risk för prostatacancer (11%) jämfört med män som hade en hög eller mycket hög nivå av fysisk aktivitet på arbetet.

Sammanfattningsvis noterade vi en något ökad risk för prostatacancer bland män med stillasittande yrken. Ur ett folkhälsoperspektiv är de observerade minskande nivåerna av total fysisk aktivitet, både med ålder och över tid (senaste 60 åren), anmärkningsvärda. Med tanke på en ökande incidens för många kroniska sjukdomar associerade med fysisk aktivitet, krävs effektiva preventiva åtgärder för att öka den fysiska aktiviteten i befolkningen.

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