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Occupational physical activity and risk of ischaemic heart disease in women – the modifying effect of leisure time physical activity, hypertension and influence at work

The Danish Nurse Cohort Study

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PREFACE

The present thesis: "Occupational physical activity and risk of ischaemic heart disease in women – the modifying effect of leisure time physical activity, hypertension and influence at work" was conducted in collaboration between the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark; Research Centre for Prevention and Health at Rigshospitalet – Glostrup and the National Research Centre for the Working Environment, Copenhagen. The thesis is based on three articles, two of which have been published and one of which is under review in international peer-reviewed scientific journals.

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The Danish Nurse Cohort Study was approved by the Ethics Committee for Copenhagen and Frederiksberg (#01-103/93) and the present study was approved by the Danish Data Protection Agency (00139/Id. No. 2001-54-0860).

List of articles:

1. Allesøe K, Holtermann A, Aadahl M, Thomsen JF, Hundrup YA and Søgaard K. High occupational physical activity and risk of ischaemic heart disease in women: The interplay with physical activity during leisure time. *Eur J Prev Cardiol* 2015; 22 (12):1601-08.

2. Allesøe K, Søgaard K, Aadahl M, Boyle E, Holtermann A. Are hypertensive women at additional risk of ischaemic heart disease from physically demanding work? *Eur J Prev Cardiol* 2016; 23 (10):1054-61.

3. Allesøe K, Holtermann A, Rugulies R, Aadahl M, Boyle E, Søgaard K. Does high influence at work modify the relation between high occupational physical activity and risk of heart disease in women? *International Archives of Occupational and Environmental Health* 2017, DOI 10.1007/s00420-017-1207-1

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1. INTRODUCTION

Cardiovascular disease (CVD) is group of disorders that affect the heart and blood vessels. The main cardiovascular diseases are ischaemic heart disease (IHD) and cerebrovascular disease (stroke)[a]. CVD is a worldwide health challenge and involves high levels of societal economic costs. CVD is presently the leading cause of death in Europe and the United States [1-4]. In Europe, IHD is the most common cause of death among the cardiovascular diseases, in both men and women [4]. IHD is caused by a complex interrelationship between large numbers of risk factors, such as physical inactivity, high blood pressure, high cholesterol and blood lipids, smoking [5] and occupational-related factors [6-8].

Modern technology has decreased the physical workload in some professions. However, many workers in Europe – both male and female – are still employed in jobs with high occupational physical activity (OPA) [9], and the physical demands of their work have been shown to exceed the physical capacity of many workers [10]. The studies by Morris et al. in the 1950s on the health impact of OPA showed that the rate of coronary heart disease was lower in workers with more physically active occupations, such as conductors, compared to those in sedentary professions, like bus drivers [11;12]. This finding, which shows a beneficial relation between being physically active at work and heart health has been confirmed in other early studies [13-17].

Nevertheless, a state-of-the-art article from 2000 stated that, although most current findings indicated that high OPA protected people from CVD, the epidemiological evidence of an association between high OPA and CVD was sparse and inconclusive [18]. A few studies actually indicated that patterns of OPA, such as irregular, heavy physical exertion alternating with sedentary work and heavy lifting could be risk factors for CVD [18], and that a higher incidence of IHD was found in occupations with high physical demands [19]. In line with these findings, a number of recent studies among men have shown that high OPA is associated with an increased risk of CVD and all-cause mortality [20-22], but there are also some contrasting findings [23]. Fewer studies have been conducted among women, of which only a small number have indicated a higher risk of CVD from high OPA. The majority of studies among women, have suggested that high OPA is not associated with CVD or all-cause mortality or could even be protective [20;23;24]. Whether high OPA is a risk factor for CVD and whether the discrepancy in findings for men and women really reflects a gender difference in the association between high OPA and CVD and mortality is still not known.

Leisure time physical activity (LTPA) is, however, well known to improve cardiovascular health and to reduce the risk of CVD and all-cause mortality. A large number of both observational and intervention studies have established this evidence [24-30]. LTPA and thereby increased physical fitness have been hypothesized to counterbalance the possible detrimental effect of high OPA on the cardiovascular system [21;31], and this has been demonstrated in some studies among men [32-34]. There

[a] http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/cardiovascular-diseases2 (15 January 2017)

are also some opposing findings [35], and the present knowledge – particularly as regards women – is not conclusive.

An editorial from 2010 about the roles of OPA, LTPA and fitness in cardiovascular mortality called for studies investigating whether sub-populations of workers, e.g., with chronic health conditions, are especially vulnerable to physically demanding work with respect to cardiovascular health [21]. Physically demanding static tasks, such as lifting and carrying, could markedly increase blood pressure and thereby impose strain on the cardiovascular system, especially in individuals with hypertension [36]. Only a few studies among men have investigated whether hypertensive individuals are particularly vulnerable to exposure to high OPA in relation to the risk of CVD [37;38 39], and no studies among women were found.

Control over how one plans and organises one's daily work could mitigate the detrimental impact of high OPA on cardiovascular health; for example, by taking breaks or having a rest when needed. On the organisational level, adapting or distributing physically demanding tasks among workers in line with their physical capacities could also regulate the impact of this kind of work. However, only one single study addressing this topic has been identified [40].

It should be noted that the majority of studies investigating the association between OPA and CVD are population-based and span a range of social classes. Social class is strongly associated with OPA; workers with high OPA tend to belong to lower social classes than workers with sedentary OPA [41]. Social class and related factors, such as occupational class and occupational category, are associated with CVD [42-44]. An association between high OPA and CVD could be explained in part, therefore, by social class or associated factors, and the independent effect of high OPA might be difficult to disentangle.

The Danish Nurse Cohort Study, established in 1993, involved a large cohort of female nurses with individual links to register-based information on incident IHD [45]. The cohort included only one single profession. Because all the nurses had the same educational background, this cohort is well suited to an exploration of the association between OPA and IHD, because there is less risk of confounding from socio-economic factors. Questions about physical activity at work and during leisure time and about other occupational factors, like influence at work, as well as many relevant risk factors for CVD were included in the 1993 questionnaire in connection with the study.

1.1 Aim

The overall aim of the thesis was to investigate the association between occupational physical activity (OPA) and the risk of ischaemic heart disease (IHD) among female nurses aged 45-64 from the Danish Nurse Cohort Study.

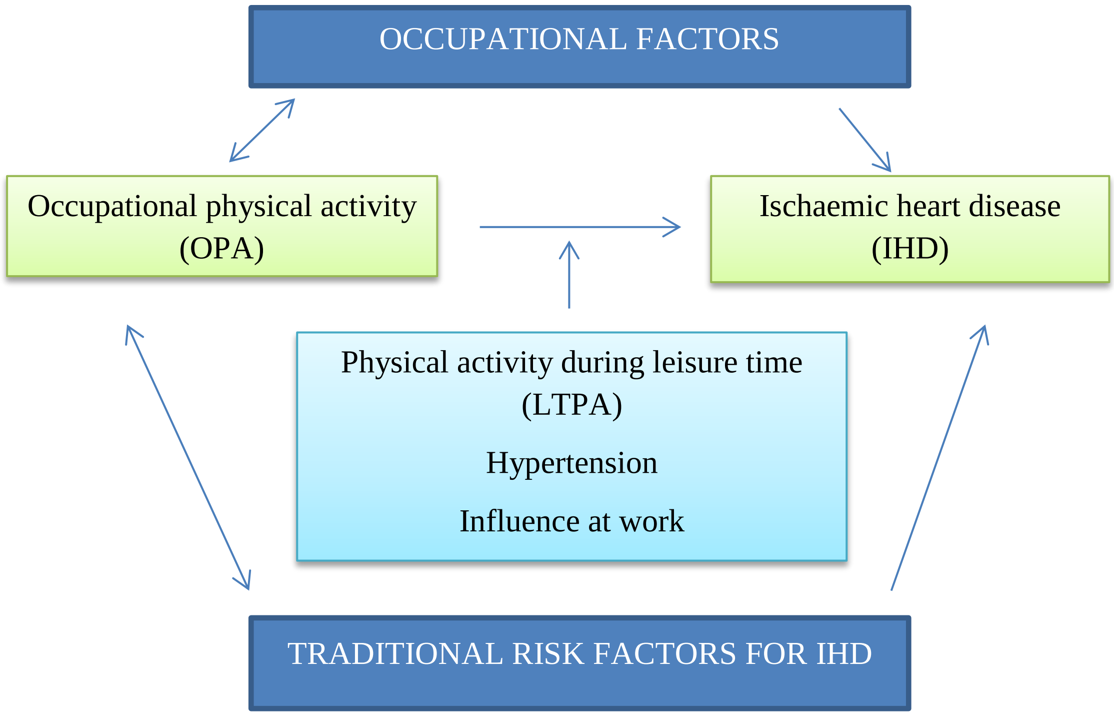
The specific objectives and hypotheses were:

- To investigate the association between high OPA and risk of IHD and whether LTPA modifies this association. *The hypothesis was that high OPA is associated with an increased risk of IHD in contrast to a beneficial effect of vigorous LTPA* (Study I a). *Furthermore, the hypothesis was that vigorous LTPA can modify and thus counteract an increased risk of IHD associated with high OPA* (Study I b).

- To investigate whether hypertension modifies the association between high OPA and risk of IHD. *The hypothesis was that the risk of IHD from high OPA is higher among women with hypertension than among normotensive women* (Study II).

- To investigate whether influence at work modifies the association between respectively high OPA and risk of IHD. *The hypothesis was that having high influence on the organisation of the daily work can counteract a detrimental association between high OPA and risk of IHD* (Study III).

Fig. 1. Conceptual model presenting the aim and hypotheses of the study



2. BACKGROUND

2.1 Ischaemic heart disease

Ischaemic heart disease (IHD) is the name for a group of acute or chronic disorders that affect the blood supply to the heart. IHD is associated with disease processes in the coronary arterial system, including atherosclerosis [46]. IHD comprises myocardial infarction (MI), angina pectoris and other forms of acute or chronic IHD [46]. There are 1.8 million deaths each year due to IHD in Europe, making this the single most common cause of death in Europe, and a major health problem in both men and women [4]. There is a gender difference in the first manifestation of heart diseases – on average, they appear 7-10 years later in life in women than in men [47].

Since the 1980s, there has been a declining trend in the incidence of, and mortality from IHD and CVD in many Western European countries [4], but the social inequality in the burden of IHD and in the distribution of risk factors for IHD remains high [42;43;48;49].

The underlying pathophysiological process that causes IHD is atherosclerosis in the coronary arteries. In atherosclerosis, a buildup of fat, cholesterol, calcium and other substances in the arterial walls narrows the lumen and might also decrease the elasticity of the artery [50]. Atherosclerosis often starts early in life and develops over the lifetime [50]. During the first silent and asymptomatic steps, which could last for decades, endothelial dysfunction leads to progressive morphological changes in small areas of the endothelium of an artery, called fatty streaks [51 52]. These can further develop into atherosclerotic plaques, if there is sustained exposure to risk factors, such as elevated levels of lipids or lipoproteins in the blood [52]. As atherosclerosis progresses, it can become symptomatic if the narrowing of the arteries limits blood flow to the heart and causes oxygen deficiency. This condition can become chronic; for example, in stable angina pectoris, a condition of impaired supply of oxygen to the heart due to narrowing of the coronary arteries that causes symptoms during exercise. There are, however, also acute events of IHD. Progressive atherosclerosis increases the risk that an atherosclerotic plaque disrupts, a blood clot (thrombus) is formed and one of the arteries becomes blocked, leading to acute IHD events, such as MI [50 52;53].

There are many known risk factors for IHD, and it is an interaction between a combination of these risk factors that, over time, leads to IHD [5;54]. The risk of IHD rises sharply with age in both men and women [46]. Some of the other important, non-modifiable risk factors are gender and family history of CVD, including genetic factors [5]. Heart diseases are largely preventable; 80-90% of IHD cases are explained by risk factors that can be prevented or treated, such as physical inactivity, smoking, alcohol, dietary factors, obesity, unfavourable profile of blood lipids, high blood pressure and diabetes [54;55]. A number of occupational factors are also associated with an increased risk of IHD and other forms of CVD [6], and it has been estimated that around 20% of incident IHD is explained by occupational factors [7;8]. High OPA is one of the possible exposures at work that has been proposed as a potential risk factor for CVD [21].

2.2. Physical activity

Definitions and categorization of physical activity

Physical activity takes place in various contexts or domains: at work, during leisure time, transportation and in doing household tasks [24]. The main focus of this thesis is on physical activity at work, which covers a range of types of muscular action, including static work. A definition of physical activity from Butte et al. is used: "All bodily actions produced by the contraction of skeletal muscle that increase energy expenditure above basal level" [56]. Physical activity is a multidimensional behavior characterized by the intensity, frequency, duration and type of bodily action, the domain, and by the pattern in which physical activity intensities appear, for example, during a working day [57;58].

Differences between OPA and LTPA

Physical activity takes place both at work and during leisure time, but there are important characteristics of OPA that differ from LTPA [57]. LTPA is characterized by being voluntary and of rather short duration. The duration, frequency and intensity are self-selected and can be adapted to individual physical capacity. LTPA most often consists of dynamic physical activity. OPA is work task-dependent and the duration of up to 7 – 8 hours each working day as regards full-time employees is significant to accumulated load. In many occupations, OPA involves dynamic as well as static work, including lifting, pushing, or pulling [57]. A relative load of 33% of maximal aerobic capacity carried out for 30-60 minutes corresponds to a moderate level of physical activity, whereas, when performed over the entire course of a full working day, it corresponds to a physically demanding job [59].

The intensity of LTPA during running, biking or swimming is often sufficiently high to improve cardiorespiratory fitness, which is the capacity of the cardiorespiratory system of an individual to transport and use oxygen during dynamic physical activity [60], and this is associated with better cardiovascular health [61]. In contrast, OPA seldom involves a sufficient degree of high intensity periods to lead to a training effect of the cardiorespiratory system [62;63], and might even have negative effects on cardiovascular health. In spite of low average force demands, static work tasks, such as lifting, pulling and pushing, can be strenuous if they are of long duration. Among health care workers, these tasks can also impose high peak workloads [59], e.g., sudden loading during patient handling. Standing for many hours puts a strain on the cardiovascular system [64;65], and even dynamic work like walking during a full work day can lead to increased cardiovascular load, e.g., increased heart rate over several hours [63]. Recovery after strenuous work can take hours or even days, after exhausting tasks [59]. In contrast to LTPA, there can be limited opportunities at work to take breaks and rest when exhausted, and there might not be the necessary time for recovery between working days.

It has been discussed whether the abovementioned differences might explain the findings in more recent studies of a detrimental impact of high OPA on cardiovascular health – in contrast to the well-known beneficial impact of LTPA [21;22].

Workload and physical capacity

The response of the cardiovascular system to a given workload depends on the individual worker's physical capacity [19]. There will be, for instance, a larger increase in heart rate among workers with low – compared to those with high – cardiorespiratory capacity during demanding work [66]. Physical capacity depends on age, body composition, cardiorespiratory fitness, genetics and gender [19;59;62]. The relationship between the external physical load and the individual physical capacity and the opportunity for rest and restitution can, over time, influence whether the level of OPA is health-promoting or having detrimental health effects for the individual [59]. Based on this knowledge, guidelines on physical activity at work from the International Labor Organization suggest that the aerobic load of the individual worker on average during an eight hour workday should not exceed 33% of the maximal aerobic capacity [67;68].

Prevalence of high OPA

Many European workers – both male and female – are still employed in jobs with high physical demands [9]. The general level of OPA in Europe is higher for men than for women, but moving and lifting of persons and repetitive movement are more frequent among women [9]. A Swedish study showed that physical work demands exceeded individual physical capacity for 27% of the studied men and 22% of the women [10]. Similarly, in a Finnish population study, around one third of the workers exceeded the recommendation for VO_{2max} for an eight-hour working day [69].

There is a high degree of gender segregation in jobs with high physical demands [70]. Accordingly, the vast majority of nurses in Denmark are women [71]. Most women working with high physical demands are employed in health or social care (70%), or in kitchen and cleaning work (14%) [70]. Nurses in Denmark have physical demands at work above the average for female workers[b], and a survey from 2006 showed that, in Denmark, many nurses still had to push or pull, lift or carry heavy loads and to work in awkward positions [72]. A more recent study showed that these demands were nearly unchanged between 2002 and 2007[c].

2.3. High OPA and risk of CVD, IHD and all-cause mortality

A number of prospective cohort studies have investigated the association between OPA and health, but the majority of them have studied men. In the following section, knowledge from prospective studies carried out from the late 1980s until now that separately analyse risks for men and women are included. They are presented in sections with CVD, IHD, MI and all-cause mortality as the respective outcomes.

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[b] http://www.arbejdsmiljoforskning.dk/da/arbejdsmiljoedata/flere-datasaet/arbejdsmiljo-og-helbred/alle-svar-for-jobgrupper/diagram?group=NAK10_Jobgrp_1104 (15 January 2017)
[c] https://dsr.dk/sites/default/files/24/notat_fysisk_arbejdsmiljoe_blandt_sygeplejersker_2012_0.pdf (15 January 2017)

High OPA and risk of CVD, IHD and MI

Among women, an increased risk of IHD from high OPA was indicated in two cohort studies [73;74], but, in contrast, three studies from cohorts in Finland showed a protective effect of high OPA with respect to risk of IHD [75], MI [15] and a protective effect of both moderate OPA and high OPA on CVD, respectively [76]. Furthermore, a number of former cohort studies did not find any association between high OPA and MI [33;77] or CVD among women [76;78;78;79].

Among men, studies in two large Danish cohorts showed that – compared to those with low OPA – those with both moderate and high OPA had an increased risk of IHD [34] or MI [33]. Correspondingly, three other studies have also shown an increased risk of CVD [74], IHD [80] and MI [81] from high OPA. In a study from Israel, an increased risk of CVD from high OPA was indicated [82] and a Belgian study found an increased risk of IHD from high OPA in the age-adjusted analysis [35]. These findings are supported by results from a Finnish study, which showed that high energy expenditure at work was associated with accelerated progression of atherosclerosis [69]. This is an important demonstration of a plausible physiological pathway from exposure to high OPA to CVD.

In contrast, a number of earlier studies found a protective effect on cardiovascular health of high OPA, compared to being sedentary at work [15-17;83]. Some more recent studies have also reported a protective effect of moderate and high OPA with respect to IHD [75] and mortality from CVD [76 78]. A study based on the Danish National Health Interview Survey from 2012 showed a decreased risk of IHD among men with high OPA, but an increased risk from heavy lifting at work [73]. In other studies, no association between high OPA and risk of CVD was found [35;79;82;84-91].

High OPA and risk of all-cause mortality

Among women, studies on the association between high OPA and all-cause mortality have overall shown no – or a protective – effect. Five recent studies showed no association between OPA and risk of death from all causes [33;73;74;92;93], but in two of the studies, a u-shaped association was suggested, with lowest risk of premature death among women with moderate OPA and higher risk among those with sedentary or high OPA [33;92]. One study showed no association between high OPA and all-cause mortality, while a protective effect of moderate OPA was found [76]. A protective effect of high OPA in relation to all-cause mortality was found in a number of the earlier studies among women [15;76-78;94;95].

Among men, studies based on three different Danish general population cohorts showed that both moderate and high OPA were associated with an increased risk of death from all causes [33;34;92]. Correspondingly, a study from Israel and a study from Taiwan both found increased risk of death from all causes among men with high OPA [74;82]. A study from Belgium indicated that moderate and high OPA could be associated with increased risk of all-cause mortality [96]. A similar trend was found in other studies [93 85 87]. However, in several studies, no association between high OPA and all-cause mortality was found [16;73;86;86;88;89;94;96]. Yet, other studies found a decreased risk of all-cause mortality from high OPA [17;76;78].

Possible difference in the health impact of high OPA among men and women

Some of the abovementioned studies that included both genders showed the same effect of high OPA on health, but only one study found a detrimental effect of high OPA in both men and women [74]. In contrast, a number of the studies found a protective or no effect of high OPA with respect to risk of IHD, CVD or all-cause mortality, among both men and women [15;75;76;78;79].

Some of the studies including both genders have, however, shown a different impact on health of high OPA in men and in women. Three studies showed a detrimental effect of high OPA on risk of IHD among men, but found no association among women [33;74;92], whereas one study found a marginally significant higher risk of IHD from high OPA among women and a lower risk of IHD from high OPA among men [73]. Statistically significant interaction between gender and OPA was found in one study, which implied that the association between OPA and mortality varied according to gender [93].

Summing up

Among women, most of the former studies showed no effect or a protective effect of high OPA in relation to risk of IHD, MI, CVD and all-cause mortality. Among men, a detrimental relation between high OPA and both IHD, MI and CVD, as well as all-cause mortality, were found in many of the most recent studies. There were, however, also several studies where no association was found and some, especially among the earlier studies, that found a protective health effect of high OPA. Some of the studies including both genders found different health effects of high OPA between men and women, but it is not well documented whether a gender difference exists.

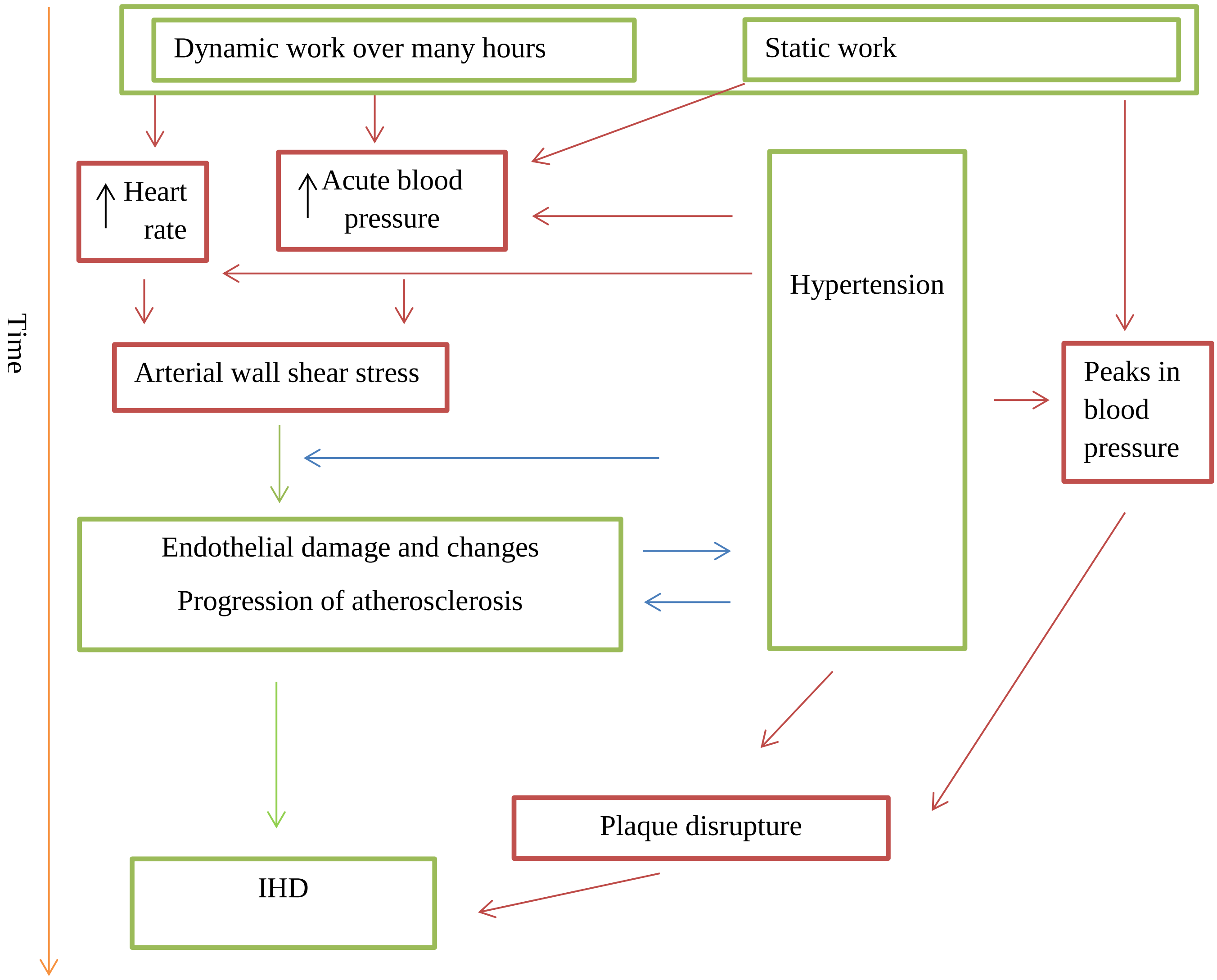
2.4. Presentation of a conceptual model of the long-term and acute effects of OPA on the risk of developing IHD

In this section, physiological mechanisms that could underlie an association between high OPA and IHD and a modifying effect of hypertension on this association are discussed. Several different hypothetical pathways could lead from exposure to high OPA to IHD, some of which are illustrated in a conceptual model in Fig. 2.

The response of the cardiorespiratory system during dynamic and static work

During exercise or work, the cardiorespiratory system reacts to the increased demand for blood flow [97]. The response of the cardiovascular system is influenced by the frequency and duration of physical activity as well as by the ratio of dynamic to static work [59;97]. In dynamic work, short contractions of the muscles alternate with relaxation. The heart rate, stroke volume and systolic blood pressure are increased and the arterioles of the skeletal muscles dilate, resulting in a net drop in the total peripheral resistance. The heart rate increases linearly with the intensity of the work, which is indicated by the oxygen consumption of the muscles (VO_2) [98]. Static muscle work causes a rise in blood pressure, but there are only small increases in heart rate and stroke volume. In static work, where the arms are above head height and during heavy lifting, the increase in blood pressure can be considerable [98]. These effects of dynamic and static OPA are illustrated by red arrows at the top of Fig. 2.

Fig. 2. Acute and long-term physiological effects of high OPA. Acute effects are marked with red, long-term effects with green and modifying effects with blue arrows



Long-term effect of OPA and hypertension on the risk of IHD

A pathway from continued exposure to high OPA over time, leading to formation and progression of atherosclerosis and further to IHD has been suggested, based on a finding that high OPA was associated with increased progression of sub-clinical carotid atherosclerosis [69]. An elevated heart rate during physically demanding work increases the time during which the heart is in the systolic phase, when unfavourable flow patterns are more frequent, and decreases the time in diastole, which is a more favourable phase [99]. The unfavourable flow patterns are complex and turbulent and cause unfavourable arterial wall shear stress and increased residence time of circulating particles [99;100]. It could also induce greater wear and tear on endothelial cells and transient mechanical disruptions of cells [100]. This could initiate inflammatory processes in the endothelium and, over time, the formation of atherosclerotic plaques [52] and, further, to an increased risk of IHD. This pathway is illustrated on the left side of Fig. 2.

Elevated daily systolic blood pressure, induced by prolonged hours of physically demanding work, could be another possible physiological mechanism of an adverse effect of high OPA – especially static work – on cardiovascular health [39;69]. Hypertension is associated with atherosclerosis [101], both in terms of the extent and severity and of the formation of plaques in locations normally free from them [99]. The combination of chronically elevated blood pressure in hypertensive individuals and a further rise in blood pressure during physically heavy work could impose a strain on the cardiovascular system, further potentiating plaque formation processes in the arteries and leading to IHD. This possible potentiating and interacting effect of hypertension on the pathway from high OPA through atherosclerosis to IHD is illustrated by the blue lines in Fig. 2.

Hypertension could also affect more directly the response and function of the cardiovascular system during strenuous work. Hypertension leads to a resetting of baroreflexes and decreased baroreceptor sensitivity [102]. This could affect the blood pressure-regulating reflex and the ability to normalize the blood pressure during and after work. At the same intensity of exercise, hypertensive individuals have higher heart rates and higher peripheral resistance than normotensive individuals. Furthermore, even mild hypertension increases the oxygen demand of the myocardium during exercise [103]. The effect of hypertension on the heart rate and acute blood pressure response to OPA is illustrated by red arrows in Fig. 2.

Acute effect of OPA on the risk of IHD

Physically strenuous work, e.g., heavy lifting or other heavy static tasks, could elicit peaks of highly elevated blood pressure. This has been observed during resistance exercise [104]. Sudden changes in blood pressure might increase the magnitude of the forces acting on the arterial wall and this has been suggested as one of the causes of the disruption of vulnerable atherosclerotic plaques [99], which could lead to MI. Studies have shown a temporary increased risk of MI after engaging in strenuous physical activity at work or in leisure time [105-107]. The acute strain on the cardiovascular system during strenuous physical tasks might be even larger among individuals with hypertension. This hypothesized acute effect of high OPA that could be potentiated by hypertension is illustrated in

Fig. 2 by the red lines – from high OPA through peaks in blood pressure to plaque disrupture and further to IHD.

2.5. Potential modifying effect of LTPA, hypertension and influence at work on the association between OPA and IHD

The following sections outline the background for a potential effect modification of LTPA, hypertension and influence at work on the association between OPA and IHD.

2.5.1. Physical activity during leisure time

One of the objectives of this thesis was to investigate whether being physically active during leisure time could protect one from a possible detrimental effect of high OPA in relation to risk of IHD. LTPA is health-promoting and a large number of studies have shown that LTPA decreases the risk of CVD and all-cause mortality [24-30;108;109]. One of the beneficial effects of LTPA in relation to cardiovascular health is that high-intensity endurance exercise improves cardiorespiratory fitness [110]. Furthermore, physical activity improves major CVD risk factors, such as unfavourable profile of lipoproteins, triglycerides, lower blood pressure and heart rate, together with improved glucose tolerance and insulin resistance, and reduced atherosclerosis [27 111-113].

It has been hypothesized that, in particular, the balance between the level of physical work demands and aerobic capacity determines the health effects of OPA [21]. Engaging in endurance and resistance training during leisure time could affect the risk of IHD from high OPA through improved fitness and the other beneficial cardiovascular effects of moderate to vigorous LTPA. LTPA could, thus, be a possible effect modifier that lowers the risk of heart disease from high physical activity at work.

Only a few former studies among women have looked into the health effects of the interplay between OPA and LTPA. A Danish study from 2012 found no increased risk of either MI or all-cause mortality from high OPA at either level of LTPA [33]. A protective effect of the combination of high OPA and a high level of LTPA and active commuting on the risk of IHD has, however, also been found [75].

More studies among men have investigated the relation between different combinations of OPA and LTPA and risk of IHD and all-cause mortality. Some of them found that a high level of LTPA seemed to counteract a detrimental association between high OPA and all-cause mortality [33 82 80;114]. A modifying effect of cardiorespiratory fitness counteracting a detrimental association between high OPA and IHD has also been found [34] and, in another study, it was found that an adverse effect of combined exposure to high OPA and low LTPA was particularly pronounced among those with low physical fitness [96].

LTPA could, therefore, potentially modify and positively affect the impact of high OPA on health through improving individual aerobic capacity and, thereby, also improve the balance between external workload and physical capacity.

2.5.2. Hypertension

Hypertension could affect the cardiovascular response and the health effects of physically demanding work – as suggested in the conceptual model in Fig. 2 (Section 2.4.). Workers with hypertension might, therefore, be particularly vulnerable to exposure to physically demanding work with respect to risk of IHD.

Hypertension, defined as a chronically elevated blood pressure above 140/90 mmHg, is one of the biggest single contributors to global mortality and burden of disease – largely through IHD and stroke [115]. Hypertension is one of the main risk factors for CVD [115;116], and each 20 mmHg difference in systolic blood pressure is associated with twofold differences in CVD death rates at age 40-69 years [117]. The prevalence of hypertension increases with age, but it is also a prevalent disease in middle-aged workers [118], and many workers exposed to high OPA could also be hypertensive. The blood pressure is increased during physically demanding work, but high OPA might also be associated with increased systolic blood pressure at home and during sleep – as was shown in a cross sectional study among both genders [39]. A prospective study has also shown an association between high OPA and an increase in blood pressure over time, as an increase in systolic blood pressure was more marked among workers with high OPA than among workers with lower levels of OPA [37].

There have been only a few previous studies among men of the impact of a combination of high OPA and hypertension on risk of IHD, CVD or all-cause mortality and none among women. A study from Finland found a more than threefold higher risk of IHD from high physical workload among men with hypertension at baseline, and an increase in blood pressure during follow-up compared to normotensive men who did not have physically demanding work, and who did not have an increase in blood pressure during follow-up [37]. In contrast, a Danish prospective study among middle-aged men showed higher risk of IHD from high OPA only among normotensive and not among hypertensive men [38]. Based on the present knowledge, it is an open question whether or not the presence of hypertension modifies the association between high OPA and IHD or CVD and, thus, whether hypertension could be a key factor in high physical workload leading to IHD [37;39].

2.5.3. Influence at work

The impact of high OPA on health may potentially also be influenced by organisational factors, such as opportunities to take breaks when needed and getting help from colleagues for highly demanding work tasks. It was one of the objectives of the present thesis to investigate if having high influence at work could reduce the risk of IHD from high OPA. In the present thesis the term influence at work cover the level of influence the worker has on the organisation of his or her daily work.

The Demand-Control model, developed by Karasek and Theorell, suggests that an imbalance between high psychosocial demands and low job control – called job strain – is associated with adverse health effects [119]. In the Demand-Control model, job control has two dimensions: skill discretion (work requiring skill, work requiring creativity, the possibility of learning new things and the level of repetitiveness) and decision authority (control over work pace, quantity of work, policies and procedures, time of breaks and scheduled hours) [119;120]. The model has been highly influential and has formed the theoretical basis of many studies investigating the association between psychosocial work factors and various health outcomes, including CVD. Studies among women of the association between job control, or one of the two dimensions of job control, and MI or IHD have shown significant positive associations in some studies [121-123] and none in others, e.g., in The Nurses' Health Study from the United States [124] and the Whitehall study [125].

It has been proposed and discussed whether high job control, as presented in the Demand-Control model, has a buffering effect on the association between high psychosocial demands and CVD, and whether an interaction effect exists [126-128]. In line with this thinking, decision authority could impact on workers' opportunities to plan and organize tasks at work and thereby their opportunity to adjust physical work demands to their personal work capacity and could thereby affect the health effect of high OPA. They could exert this authority by, for instance, having control over breaks at work and taking the opportunity to distribute strenuous tasks over the working day to allow for recovery between bouts of exertion. These possibilities could be linked both to aspects of job control and social support. Decision authority could also be related to opportunities at the workplace to be transferred to less strenuous tasks when the physical work demands exceed individual physical capacity, e.g., with increasing age or in relation to the development of chronic disease, such as CVD.

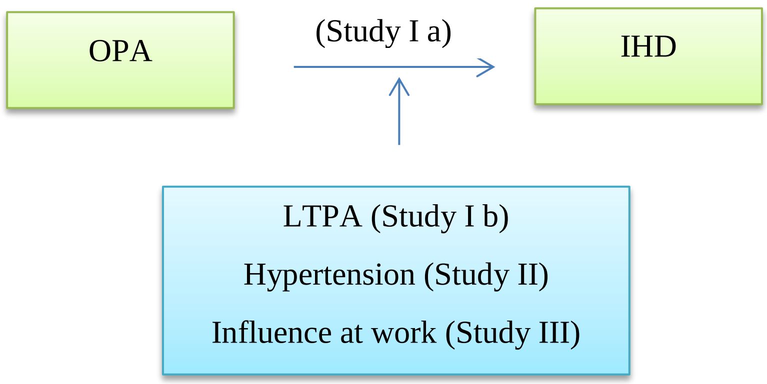
The possible health effect of the combined exposure to psychosocial work factors and OPA has been investigated in relation to health outcomes like musculoskeletal disorder [129;130]. Only two previous studies have been identified that investigated the possible buffering effect of psychosocial work factors on the association between high OPA and IHD. One study from Sweden found that the standardised hospitalisation ratio for MI was higher among male workers in the case of a combination of hectic work and heavy lifting than from heavy lifting alone [131]. A recent study from Belgium investigated the potential buffering effect of job control and social support at work on the association between physical work demands and IHD. The authors found no difference in the association between high OPA and IHD dependent on the level of job control [40]. However, a buffering effect of social support was shown [40].

Because so few studies have investigated the joint effect of OPA and psychosocial work factors on cardiovascular health, it is not yet known whether a high level of influence at work might counteract a detrimental association between high OPA and risk of IHD.

3. MATERIALS AND METHODS

The thesis comprises three studies, Studies I, II and III, in which the specific objectives set out in Section 1.1 and some additional analyses were investigated.

Fig. 3. Illustration of the objectives in Studies I, II and III



3.1 Materials

3.1.1 The Danish Nurse Cohort Study

Population

The Danish Nurse Cohort Study involved females aged 45 years and above who were members of the Danish Nurses' Association. The majority of the nurses (around 95%) in Denmark are members of this association [45].

All nurses working in Denmark are state registered. They have the same education and belong to salaried employees class II [132]. The profession of nurses in Denmark does not include nurses' aides or auxiliary nursing staff. Danish nurses are employed in hospital service (60%), nursing homes or in municipal home care (30%); the remaining 10% are employed in, e.g., education and private employment [133].

Baseline and follow-up surveys

In 1993, the population of Danish female nurses aged 45 or older (n=23,170) received by post a comprehensive, self-administered questionnaire on demographics, health and lifestyle, including questions on occupational status and working. A follow-up survey was done in 1999, which included the majority of the questions from the 1993 questionnaire.

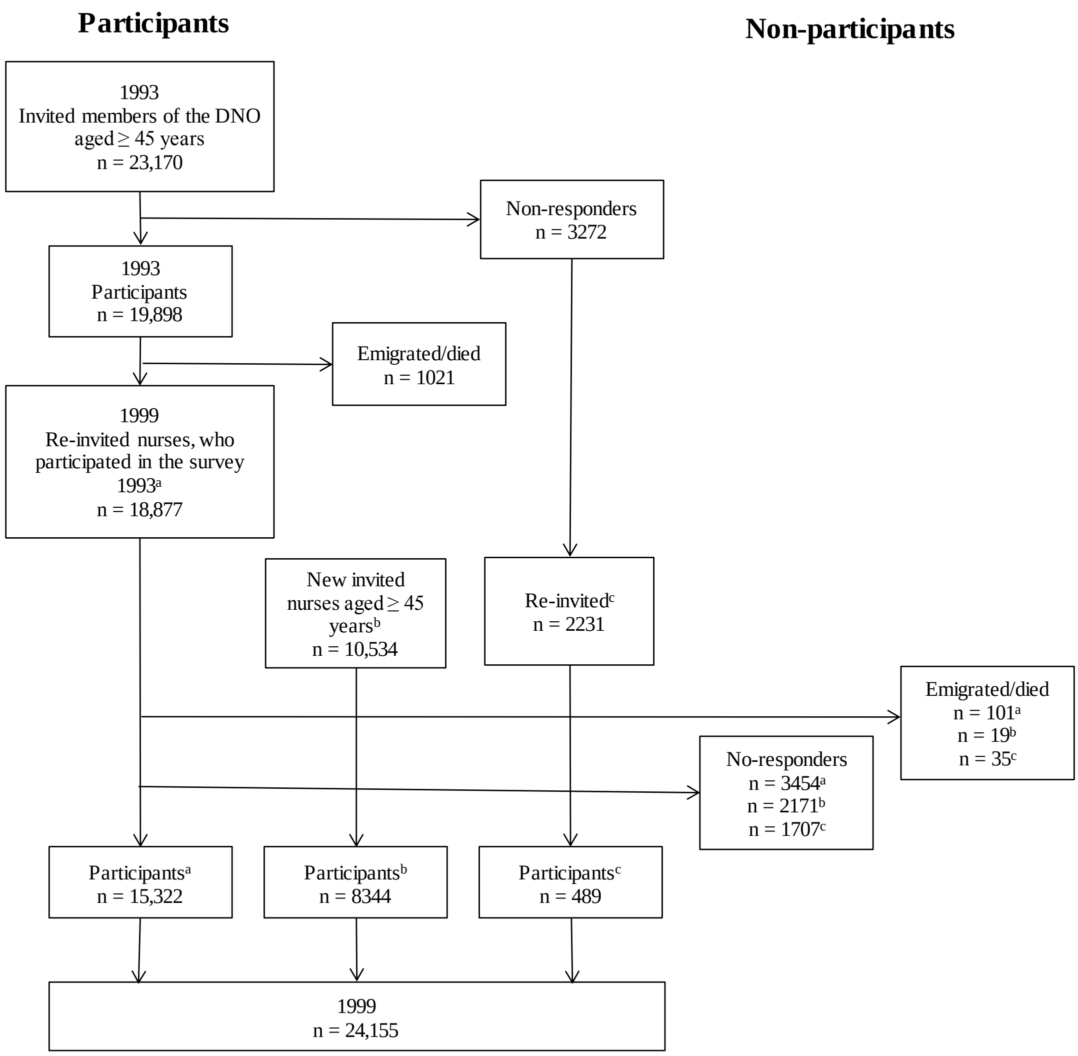
In the present study, data from the 1993 survey was used for the main analyses and data from the 1999 survey for some of the sensitivity analyses (described in section 3.2.1).

Participants in the 1993 and 1999 surveys

In Fig. 4, a flowchart of the 1993 and 1999 surveys is shown. Overall, 19,898 (86%) of the 23,170 invited nurses in the 1993 survey and 24,155 (76%) of the 31,642 invited nurses in 1999 returned the questionnaire.

In 1999, a total of 18,877 nurses from the 1993 survey (all participants apart those who had died or had emigrated) and 2231 of the non-respondents (excluding those who, in 1993, declined to participate) from the 1993 survey were invited to participate. Furthermore, an additional 10,534 nurses, who had turned 44 since 1993, were invited. A total of 15,322 participated in both surveys, and, in total, 28,731 participated in 1993 or 1999 or in both surveys (Fig. 4).

Fig. 4. Flowchart of participants and non-participants in the 1993 and 1999 surveys

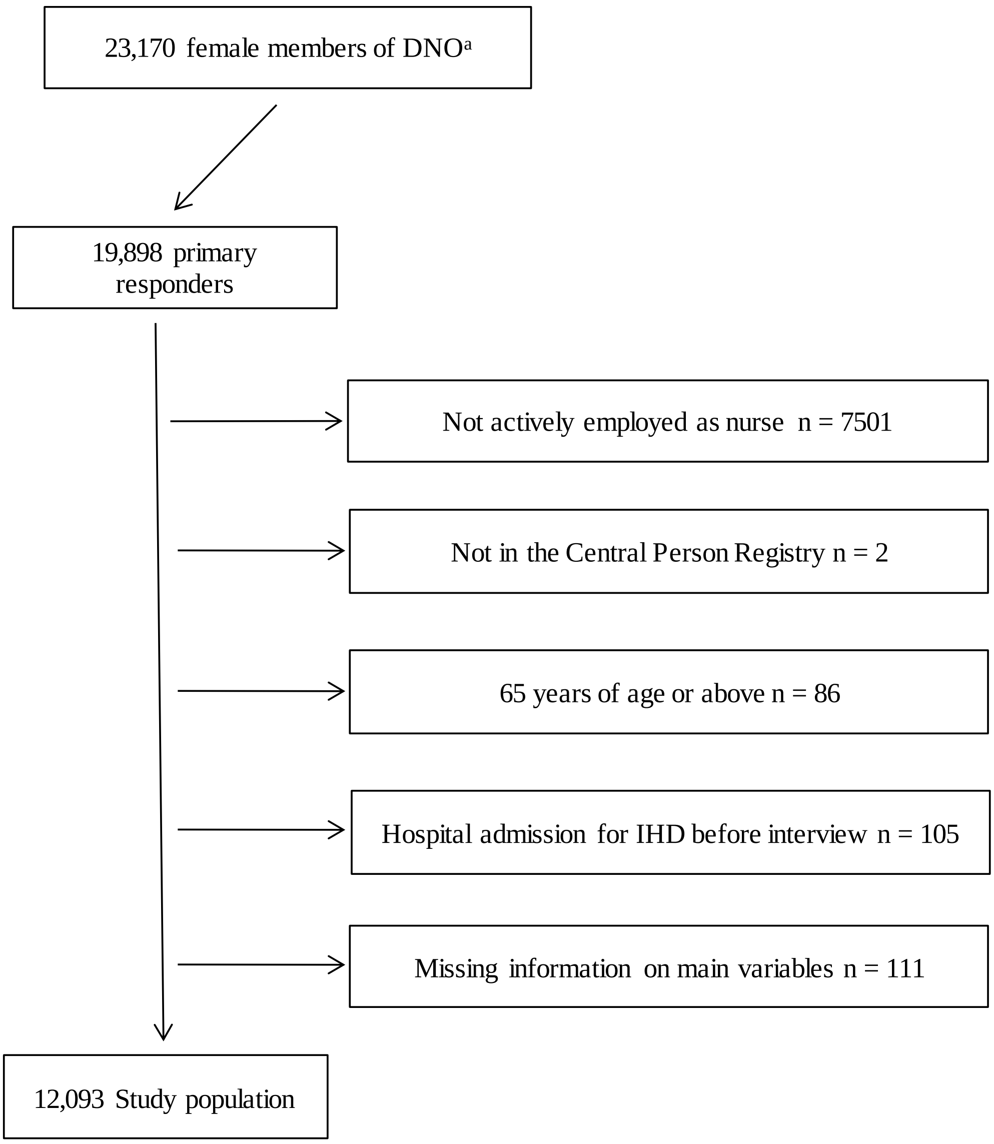


[a]Re-invited participants; [b]new invited participants; [c]non-responders in 1993 and re-invited in 1999.
DNO: Danish Nurses' Association

3.1.2. Thesis study population and exclusion criteria

Out of the 19,898 participants in the Danish Nurse Cohort Study 1993 survey, nurses who were not actively employed as nurses at baseline (n=7,501) or who had passed retirement age, which at the time was 65 (n=86), were excluded. Based on registry data, a further 105 women who had a hospital admission for IHD prior to their baseline survey and two women who completed the questionnaire, but were not registered in the Danish Central Person Registry (see 3.1.3) at baseline were excluded. Additionally, women with missing information on physical activity at work and psychosocial work factors were excluded (n=111). Therefore, the study population comprised 12,093 women. (A flowchart is shown in Fig. 5).

Fig. 5. Study population in 1993



[a]Danish Nurses' Association

3.1.3 Administrative databases

Two Danish nationwide registers were used in this thesis, both of which are based on the personal identification number allocated to all residents in Denmark. The register data was combined with the survey data using individual personal identification numbers.

The first register was the Central Person Registry. It contains basic personal information on all Danish residents. Information about age, date of death and date of emigration was obtained from this register.

The second register was the Danish National Patient Registry. It contains information on all admissions to Danish hospitals [134]. In the Danish National Patient Registry, diagnoses were classified according to ICD-8 (three-digit codes in a modified Danish version with two supplementary digits) from 1977 until the end of 1993. From 1994, ICD-10 codes were used (five-digit codes) [134].

In Denmark, patients treated in general practice are not registered in central registries.

3.1.4 Defining the endpoint

The endpoint in all three studies was incident hospitalisation with IHD. IHD cases were classified according to the WHO International Classification of Diseases (ICD 8 and 10)[d] as first-ever hospitalisation with MI (410 in ICD-8 and I21-23 in ICD-10), other acute or chronic IHD (411-412 in ICD-8 and I24-25 in ICD-10), angina (413 in ICD-8 and I20 in ICD-10) or electrocardiographically-diagnosed heart disease (414 in ICD-8).

Information about the outcome in this study was retrieved from registries as described in 3.1.3. This information generally has a high validity and is not connected with information about exposure. Information about incident IHD was based on information about first-time hospitalisation with IHD and includes both hospitalised fatal and non-fatal cases. This means that deaths out of hospital caused by IHD and cases of IHD not treated at the hospital were not included as cases. The reason for choosing hospitalisation with IHD as outcome and not including deaths from IHD out of hospital was that the diagnoses in the Danish National Patient Registry are considered more valid than diagnoses in the National Registry of Deaths [135]. The overall quality of the data in the Danish National Patient Registry has been evaluated and the medical diagnoses were correctly categorized in 73% of the cases, using the three-digit level and in 81% of cases when two secondary diagnoses were included [134]. Studies of the validity of individual diagnoses have been performed for some of the diagnoses included in the present study. For MI, several studies have shown a positive predictive value over 92.4, with one exception, including data from emergency patients where the positive predictive value was 81.9 [134].

[d] http://www.who.int/classifications/icd/en/ (15 January 2017)

Some of the less severe cases of IHD, especially angina pectoris, are treated out of hospital in general practice [136] and are thus not included as endpoints. Therefore, a sensitivity analysis was performed to investigate whether the exclusion of angina from the outcome affected the association between OPA and IHD.

3.1.5. Variables of interest

Information on OPA, LTPA, demographics, and a number of known risk factors for IHD and occupational factors was self-reported by questionnaire in 1993. In some additional analysis (described in Section 3.2), a number of questions from the 1999 survey were used. The questions used are shown in Appendix 1.3.

In Table 1, a list of variables and outcomes used in the three studies and in the additional analyses is shown. Below the table, there is a description of each of the variables and outcomes.

Table 1. List of variables used in Studies I, II and III and in the additional analyses

	Study I	Study II	Study III	Additional analyses
Predictor	OPA (sedentary, moderate, high)	OPA (sedentary, moderate, high)	OPA (sedentary, moderate, demanding, strenuous)	OPA
Outcome	IHD IHD except angina pectoris	IHD	IHD	IHD
Possible effect-modifier	LTPA	Hypertension	Influence at work	
Possible confounders	Age Smoking Alcohol intake BMI Diabetes Family history of IHD Influence at work Work pressure Working hours per week Shift work	Age Smoking Alcohol intake BMI Diabetes LTPA Family history of IHD Influence at work Work pressure Working hours per week Shift work Hypertension	Age Smoking Alcohol intake BMI Diabetes LTPA Family history of IHD Working hours per week Shift work	Age Smoking Alcohol intake BMI Diabetes LTPA Family history of IHD Influence at work Work pressure Working hours per week Shift work
Variables for sensitivity analyses	Self rated health	Use of anti-hypertensive medication	Work pressure	Civil status (1993 and 1999) Household income (1999) OPA (1999)

Predictor:

OPA was assessed by a four-class question based on Saltin and Grimby's OPA question [137;138]. The OPA question was: Which description most precisely covers your pattern of physical activity at work? The four classes were: a) mainly sedentary work without any physical exertion (“sedentary”), b) work that to a large extent is carried out standing or walking, but is otherwise not physically exerting (“moderate”), c) standing or walking work that involves some lifting or carrying (“demanding”), d) heavy or fast and physically exerting work (“strenuous”).

For the analyses in Studies I and II, the categories (“demanding”) and (“strenuous”) were merged together because of the relatively small number of nurses in the strenuous OPA category (d). This merged category is referred to as “high”.

Moderate physical activity at work was chosen as the reference group, because the knowledge at that time indicated that both high levels of physical activity at work [20;21] and high total sitting time and sedentary work [139;140] could increase the risk of CVD and all-cause mortality. Furthermore, a study had shown that women in primary sedentary occupations had a higher risk of all-cause mortality than those in occupations with standing or walking OPA [141].

Possible effect modifiers:

LTPA was assessed by a single question constructed by Saltin and Grimby [137]: “During leisure time, which statement best describes your physical activity?” a) Read, watch television or engaged in other sedentary activity (“sedentary”), b) Go for a walk, use your bicycle, or perform light physical activity (“moderate”), c) Are an active athlete or performing heavy gardening, housework, etc. for at least four hours per week, d) Vigorous training and participation in competitive sports several times a week. The categories (c) and (d) were merged in the analyses and referred to as “vigorous”.

Hypertension was self-reported from a single question: “Are you now suffering from, or have you previously suffered from hypertension?” a) Yes, b) No.

Influence at work was assessed by a single item: What level of influence do you normally have on the organisation of your daily work? a) High influence, b) Some influence, c) Very low influence or d) No influence. We dichotomised the variable into the categories of “high” (category a) and “low” (the categories b, c and d merged).

Possible confounders:

Age at the time of the interview in 1993 was retrieved from the Central Person Registry. In the descriptive analyses, age was included as a categorical variable in the categories: 45 – 49 years, 50 – 54 years, 55 – 59 years or 60 – 64 years. In one descriptive analysis, age was included as a continuous variable.

Known risk factors for IHD:

Body mass index (BMI) was assessed from self-reported questions on height and weight and was calculated as weight in kilograms divided by square of height in metres) and was divided into the

BMI categories: less than or equal to 18.5, between 18.5 and 25, from 25 up to 30, and 30 and above.

Smoking Was assessed from the question: "Do you smoke?" The categories were: never, former, current (daily/not daily).

Alcohol intake per week (Wk) was assessed from two questions: Bottles of beer, and glasses of wine and spirits on the last weekday (Monday through Thursday) multiplied by four plus the consumption the previous weekend (Friday through Sunday). A bottle of normal beer in Denmark, a standard glass of wine and spirits contains approximately 12g or 1 unit (U) of alcohol. A bottle of strong beer contains approximately 1.5 U of alcohol. The number of bottles of strong beer was multiplied by 1.5. The categories were: no alcohol intake, 1 – 28 U/Wk, >28 U/Wk in Study I and II, and, in Study III and the additional analyses: no alcohol intake, 1 – 14 U/Wk, 15 – 21 U/Wk, < 21 U/Wk.

LTPA was assessed and categorized as above.

Family history of cardiac disease: Female relatives (mother, grandmother, sister, aunt, cousins) with MI before age 65 with the categories yes (one or more), no, or unknown.

Diabetes: "Are you suffering from, or have you previously suffered from diabetes?" with the categories yes and no.

Occupational factors:

Work pressure was assessed by a single item: "What is the work pressure/work speed at your work?" categorised as a little or much too low, suitable, a little too high or much too high.

Influence at work was assessed by a single item, as shown above, and was categorised as high, some, very low or no influence in the analyses where this variable was included as a possible confounder.

Work hours per week were assessed by a single item: "Normal number of work hours per week. If the work hours are not fixed, then write the average weekly work hours". The variable was categorised as 1 – 29 hours per week, 30 – 40 hours per week, more than 40 hours per week.

Shift work was assessed by a single item: "What shifts do you usually work?" The categories were day, evening, night, or rotation.

Variables for sensitivity and additional analyses:

Self-rated health was assessed by a single question: "In general, would you say that your health is very good, good, moderate, bad or very bad?" It was categorised as very good, good, moderate or bad/very bad.

Use of anti-hypertensive medication was assessed by a single item: "Have you used anti-hypertensive medication during the previous two weeks". It was categorised as yes or no.

Civil status was assessed by two questions: “What is your civil status?” with the categories: (Married, separated, divorced, unmarried or widow) and “Are you cohabiting with a partner” with the categories: (yes or no). These two questions were merged into a single item and categorised as married/cohabiting or single.

Household income in 1999 was assessed from a single item: “What was the total income (you, spouse/partner and children living at home) of the household in 1998?” and categorised in < DKK 199,000, DKK 200,000 – 399,000, DKK 400,000 – 599,000 or > DKK 600,000.

3.1.6. Validity of variables of interest

All questions in the Danish Nurse Cohort Study questionnaire were based on well-known and tested questions from surveys of health and ill health from the National Institute of Public Health [71]. Before the 1993 survey, two pilot studies were performed to investigate the face validity of the questions [71].

3.2. Methods

3.2.1. Methods and sensitivity analyses for Studies I, II and II and additional analyses

The design of the study is a prospective, register-based cohort study. In Studies I and II, the nurses were followed over 15 years from 1993 until February 2008 and, in Study III, for 20 years from 1993 until November 2013.

In Table 2, the methods and sensitivity analyses for each study and additional analyses for the thesis are outlined. The additional analyses are described below the table.

Table 2. Table of methods and sensitivity analyses

	Study I	Study II	Study III	Additional analyses
Follow up	15 years	15 years	20 years	20 years
Descriptive statistics	Pearson chi^2 test Kruskal-Wallis test	Pearson chi^2 test	Pearson chi^2 test	Contingency tables (frequencies)
Bi- and multivariate analyses	Cox PH analysis	Cox PH analysis	Cox PH analysis	Cox PH analysis
Interaction analyses	Cox PH model including an interaction term (Wald chi^2 test) Presented as: 1) Stratified analysis 2) Analysis with common reference group	Cox PH model including an interaction term (Wald chi^2 test) Presented as: 1) Stratified analysis 2) Analysis with common reference group 3) RERI* 4) Additive hazards model	Cox PH model including an interaction term (Wald chi^2 test) Presented as: 1) Stratified analysis 2) Analysis with common reference group 3) Additive hazards model	
Sensitivity analyses OPA – IHD association	IHD apart angina pectoris as outcome Exclusion of nurses with poor/very poor self-rated health	Stratification by use/ no use of anti-hypertensive medicine Adjustment for hypertension	Censoring at age 70 years Adjustment for work pressure Possible effect modification by work pressure	Nurses with the same OPA exposure in 1993 and 1999 Adjustment for civil status
Other analyses				Change of exposure between 1993 and 1999

§RERI: Relative excess risk due to additive interaction

Additional analyses

Apart from the main analyses and the sensitivity analyses performed in each of the three studies, the following additional analyses were made:

I. Analysis of change of exposure between 1993 and 1999: The study population comprised 7,029 nurses who participated in both the 1993 and 1999 studies and who had answered the OPA question in both 1993 and 1999 (see Results section 4.7.1, Table 9).
II. Sensitivity analysis of the association between OPA and IHD among nurses with the same level of OPA exposure in 1993 and 1999: The study population comprised 4,603 nurses from the 1993 study population who had the same OPA exposure in 1993 and 1999 (in the categories: sedentary, moderate, and high) (see Results section 4.7.2, Table 10).
III. Sensitivity analysis of the association between OPA and IHD adjusted for civil status in 1993 (see Results section 4.7.3).

3.2.2. Statistical methods

In all the analyses, $p<0.05$ (two tailed test) was considered statistically significant. All statistical analyses were performed using the statistical package SAS version 9.3 and R 3.2.2.

All variables were kept as categorical variables throughout the analyses, except for age, which, in one analysis was included as a continuous variable. For both the predictor variable and all covariates, the category anticipated to pose the lowest risk of IHD was chosen as the reference category.

Descriptive analyses

In the descriptive analyses of distribution of variables in the study population, percentages were provided. In the analyses of the distribution of variables by level of OPA, hypertension status or influence at work percentages were provided and Pearson chi-squared test was used to test for associations between categorical variables, and the Kruskal-Wallis test to test for associations between continuous (age) and categorical variables.

Multivariable analyses

Cox proportional hazards models (Cox PH models) were used to test for association between IHD and predictors, between possible effect modifiers and IHD, and between included covariates and IHD. In all Cox PH models, hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Covariates considered *a priori* as possible confounders for the association between OPA and IHD based on current knowledge of their association with increased risk of CVD were included in the multivariable Cox PH models [142]. References for studies finding an association with CVD are provided after each possible confounder or set of confounders: they comprised a number of known risk factors for IHD [1], work pressure [125;143], job control [18;121;122;144], work hours [145-147] and shift work [148].

Work pressure was associated with both OPA and influence at work in this study population and was therefore not included in the fully adjusted analyses of the joint effect of OPA and influence at work in Study III. Instead, sensitivity analyses were performed, in which work pressure was adjusted for and where possible interaction between work pressure, OPA and influence at work was investigated.

Missing data

The main focus from the beginning of the study was on the joint effect of OPA and psychosocial work factors on the risk of IHD and, therefore, only nurses with complete information about OPA and psychosocial variables were included in the study. This inclusion criterion was kept in all three studies.

Missing data about the covariates reduced the number of nurses in the multivariable analyses. To investigate if this affected the association between OPA and IHD, an age-adjusted Cox PH model – including only those with complete information on all covariates – was performed and compared to the age-adjusted analysis including all 12,093 nurses. This resulted in only a slightly altered estimate.

Cox proportional hazards model

The Cox PH model is a time-to-event or survival analysis. The analysis uses survival time, which is the time for each individual from entry until an event happens (event), or when they are no longer at risk of the event, e.g., if they die during follow-up or when the study ends (censoring). The analysis is thus based on the actual time at risk for each participant in the study [149]. The probability of surviving through each successive time interval of the follow-up period, given survival up to this time, is calculated. The overall survival probability is equal to the cumulative product of the probabilities of surviving through each successive interval [142]. For cases, the time from the beginning of the study until event is known. For non-cases, the time from the beginning of the study until censoring is known. It is, however, not known whether non-cases experience the event after the study has ended. Therefore, similar studies with different follow-up times can have different results.

The Cox PH model is an expression for the hazard of an event at time t for an individual with a given set of predictor variables. These predictor variables are modelled to predict the hazard of an individual with this specific set of predictors. This can be written as:

$$h(t, \boldsymbol{X}) = h_0(t)\exp\left(\sum_{i=1}^{p} \beta_i X_i\right)$$

where $\boldsymbol{X} = (X_1, X_2, X_3, \ldots X_p)$ are a number of (p) predictor variables

This equation shows that the hazard at time t is a product of $h_0(t)$, which is a baseline hazard function, and an exponential expression e to the linear sum of $\beta_i x_i$ over p explanatory variables. The baseline hazard function is the hazard when all the Xs are equal to zero and represents a reference point that depends on time [149]. As this baseline hazard function is an unspecified function, the Cox PH model is a semi-parametric model. Semi-parametric models are robust models, and preferred, when the correct parametric model is not known [149]. The hazard ratios and survival curves can by calculated without estimating the baseline hazard function [149].

In the present study, each of the nurses from the study population are included in the analyses, with their actual risk time from baseline until first ever hospitalisation with IHD (cases), or until the time of censoring: At the time they die, either out of hospital or in hospital from other causes than IHD, at the time of emigration or at the end of follow-up, whichever occurs first.

In Cox regression analysis, the following types of variables are used: 1) time until event or censoring, 2) indicator of censoring (1, 0), where 1 is event and 0 is censoring, 3) predictor variable and covariates.

In the Cox PH model, the exponential expression is time-independent, which is the basis for the proportional hazards assumption: that the ratio of the hazards functions for any subgroups (which are groups with different values for the explanatory variable) is constant over follow-up time, all other covariates being equal. The proportional hazards assumption is the key assumption in the Cox PH model, and was evaluated in the present study for all variables by comparing estimated log-log survivor curves over the different categories of variables being investigated and by inspecting plots of Schoenfeld residuals [149].

Age was chosen as the underlying timescale and thus was implicitly adjusted for. It is recommended to have age as the underlying timescale for outcomes like IHD where age is a stronger determinant of outcome than time on study [150].

A cumulative incidence curve that takes competing risk into account [151] (death from other causes than IHD at the hospital or death out of hospital) was used for illustration of the probability of an event with increasing age during follow-up in the four categories of OPA.

The statistical significance (type 3 test) of the variables and interaction terms was assessed by the Wald chi-squared test. If the 0-hypothesis that x_i is not related to the outcome is rejected, then $\exp(\beta_i)$ (the hazard ratio (HR)) is an estimate of the ratio of the hazard at which the event occurs in the group X=1 (with exposure), relative to the hazard at which the event occurs at the same time in the group X=0 (without exposure), all other covariates being equal [149].

Effect modification and interaction

Effect modification occurs when the effect of one exposure varies by the level of another variable [152]. The term 'interaction' is often used interchangeably with effect modification [153], and both terms are also used interchangeably in the three articles and this thesis. Interaction in a biological sense means that the presence of one cause of a disease influences the effect of another cause and indicates that two exposures could be part of the same mechanism that leads to a disease.

The association between OPA – combined with, respectively, LTPA, hypertension or influence at work – and risk of IHD are presented both as separate effects and with a common reference group of the joint exposures, as recommended by the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement [154;155]. Moreover, HRs are presented for the association between OPA and IHD within strata of the possible effect modifier, and measures of effect modification on both additive and multiplicative scales are presented, as further suggested by Knol and VanderWeele [156].

Multiplicative interaction

The interaction on a multiplicative scale between physical activity at work and possible effect modifiers was investigated in Cox models by including a term of interaction between OPA and the possible effect-modifier and by testing departure from multiplicativity by using the Wald chi-square test. When there is no interaction term in a Cox PH model, a multiplicative relation between disease rates is implied. This means that the HR of a health outcome in a group with exposure to two risk factors is the product of the HR's of each of the risk factors. When an interaction term is included in the Cox PH model – and it is statistically significant – then deviation from this multiplicativity is implied and the HR in the group with double exposure deviates from the product of the two HRs [157;158].

From a Cox PH model including an interaction term between OPA and the effect modifier the following results are presented: 1) HR's for the risk of IHD from different combinations of OPA and the effect modifier with a common reference group. For this analysis, a new variable was created with different combinations of levels of OPA and the effect modifier; 2) HR's of the association between OPA and IHD in strata of the effect modifier with a separate reference group for each stratum. The Wald chi-square test was used to test for multiplicative interaction. The two ways of presenting the results from the Cox PH model including an interaction term illustrates different aspects of the associations. Since the results in 1) and 2) are results from the same model, the HR's for combinations compared to the same reference group are equal.

Analyses of the association between OPA and IHD in strata of the possible effect modifiers without the interaction term in the model were also performed.

In Study I, only the multiplicative interaction was examined, while in Studies II and III the interaction was measured both on the multiplicative and additive scales.

Additive interaction

In inherent additive models, such as the linear regression model or the additive hazards model, departure from additivity is tested. The measure of multiplicative interaction is a relative measure and the measure of additive interaction is an absolute measure of the impact of an interaction between two exposures.

Interaction on an additive scale was investigated using two different methods. The first was to assess the additive interaction from the inherent multiplicative model of Cox PH model. This was done by calculating the relative excess risk due to additive interaction (RERI) and testing whether this differed from zero.

1) RERI is measured from the outcome of a model with a common reference group of two exposures and is the HR of the group with double exposure HR_{11} minus the HRs in the two groups with only one of the two exposures (HR_{10} and $HR_{01)}$ plus the baseline risk in the double unexposed group (HR_{00}) which is 1. RERI = $RR_{11} – RR_{10} – RR_{01} + 1$. A RERI >0 indicates that the combined effect of the two exposures exceed the sum of their separate effects (assuming monotonic effects of both exposures) [142;159].

This measure was calculated for Study II along with the 95% confidence interval (CI). The CIs were calculated based on the method for a categorical variable with two or more levels [159].

The second method for testing for additive interaction was modelling an additive hazards model that estimates the absolute effect sizes and the absolute size of deviation from additivity [158].

The additive hazards model, like the Cox PH model, is a flexible semi-parametric model. The model consists of an unspecified baseline hazard function ($\gamma_0(t)$) plus the predictor variables (E_1 and E_2) plus a vector of potential confounders (here expressed as C) modelled as a linear function:

The hazard at time t is: $\gamma_0(t) + \beta_1 E_1 + \beta_2 E_2 + \beta_3 (E_1 \times E_2) + \beta_4 C$

The β’s are estimates of the number of additional cases per time (e.g., a number of person-years) among the exposed and is a measure of the absolute effect of exposure [158].

This model was applied in Studies II and III.

4. RESULTS

This chapter presents the main findings from the investigation of the objectives of the thesis (Studies I, II and III, as shown in Fig. 3 in the Materials and Methods section), together with results from additional analyses performed to further elucidate the hypotheses. Detailed results can also be found in Articles 1, 2 and 3.

4.1 Description of the study population at baseline

Table 3, below, shows the baseline characteristics of the study population with respect to the main variables and the covariates included in the adjusted analyses and in sensitivity analyses (number and percentage), and the number and percentage of cases of IHD.

The distribution of covariates included in the analyses by level of OPA at baseline is shown in Table 1 in Article 1 and by level of hypertension in Table 1 in Article 2.

Table 3. Baseline characteristics and number and frequency of incident cases of ischaemic heart disease (IHD) among 12,093 Danish nurses from the Danish Nurse Cohort Study, followed from 1993 for 15 and 20 years, respectively. There were 580 incident cases of IHD with 15 years follow-up and 869 cases

		Participants		IHD cases 15 years		IHD cases 20 years	
		No.	%*	No.	%**	No.	%**
Age	45 – 49	4898	40.5	159	3.2	238	4.9
	50 – 54	3427	28.3	159	4.6	235	6.9
	55 – 59	2966	24.5	199	6.7	300	10.1
	60 – 64	802	6.6	63	7.8	96	12.0
Civil status	Married/cohabiting	9448	78.1	429	4.5	643	6.8
	Single	2591	21.4	149	5.8	221	8.5
	Missing	54	0.5	2	3.7	5	9.3
OPA	Sedentary	2331	19.2	96	4.1	139	6.0
	Moderate	4159	34.3	160	3.8	257	6.2
	Demanding	4965	41.0	282	5.7	407	8.2
	Strenuous	638	5.3	42	6.6	66	10.3
LTPA	Vigorous	3290	27.2	139	4.2	225	6.8
	Moderate	8069	66.7	393	4.9	582	7.2
	Sedentary	649	5.4	44	6.8	57	8.8
	Missing	85	0.7	4	4.6	5	5.9
Familial predisposition of IHD	Yes	691	5.7	61	8.8	83	12.0
	No	10,091	83,4	437	4.3	670	6.6
	Unknown	1233	10.2	78	6.3	111	9.0
	Missing	78	0.7	4	5.1	5	6.4
Diabetes	Yes	103	0.9	20	19.2	21	20.4
	No	11,925	98.6	556	4.7	844	7.1
	Missing	65	0.5	4	6.1	4	6.1
Self-rated health	Very good	4912	40.6	157	3.2	258	5.2
	Good	5345	44.2	284	5.3	419	7.8
	Moderate	1291	10.7	104	8.1	145	11.2
	Bad/very bad	137	1.1	15	10.9	18	13.1
	Missing	408	3.4	20	4.9	29	7.1
Hypertension	Yes	1400	11.6	140	11.7	190	13.5
	No	10,638	88.0	436	4.1	675	6.3
	Missing	55	0.4	4	7.3	4	7.3
Body Mass Index	≤ 18,5	294	2.4	13	4.4	26	8.8
	>18,5 – 25	8529	70.5	374	4.4	532	6.2
	≥25 – <30	2626	21.7	146	5.6	234	8.9
	≥30	605	5.0	47	7.7	75	12.4
	Missing	39	0.4	0	0	0	0
Smoking	Current smoker	4472	37.0	269	6.0	393	8.8
	Former smoker	3062	25.3	125	4.0	202	6.6
	Never smoker	4058	33.6	161	4.0	393	6.0
	Missing	501	4.1	25	5	30	6.0
Alcohol intake	No alcohol intake	1656	13.7	102	6.2	144	8.7
	1-28 units/ Week	8465	70.0	372	4.4	595	7.0
	> 28 units/Week	1424	11.8	77	5.4	93	7.9
	Missing	548	4.5	29	5.3	37	8.4
Work pressure	Suitable	4639	38.4	193	4.2	295	6.4
	A little too high	5673	46.9	287	5.1	438	7.7
	Much too high	1664	13.8	94	5.6	128	7.7
	Much/a little too low	117	1.0	6	5.5	8	6.8
Influence at work	High influence	4776	39.5	216	4.5	322	6.7
	A certain influence	6051	50.0	303	5.0	457	7.5
	Very low influence	1072	8.9	46	4.3	70	6.5
	No influence	194	1.6	15	7.7	20	10.3
Shift work	Day	7406	61.3	341	4.6	512	6.9
	Evening	1502	12.4	80	5.3	117	7.8
	Night	937	7.7	69	7.4	95	10.1
	Rotate	2238	18.5	90	4.0	145	6.5
	Missing	10	0.1	0	0	0	0
Work hours per week	1 – 29 hours	3540	29.3	172	4.9	260	7.3
	30 – 40 hours	8077	66.8	383	4.7	581	7.2
	> 40 hours	416	3.4	23	5.5	24	5.8
	Missing	60	0.5	2	3.3	2	3.3

**These percentages represent the number of nurses in the category/12,093 ×100; **These percentages represent the number of IHD cases in the category/number of nurses in the category×100.*

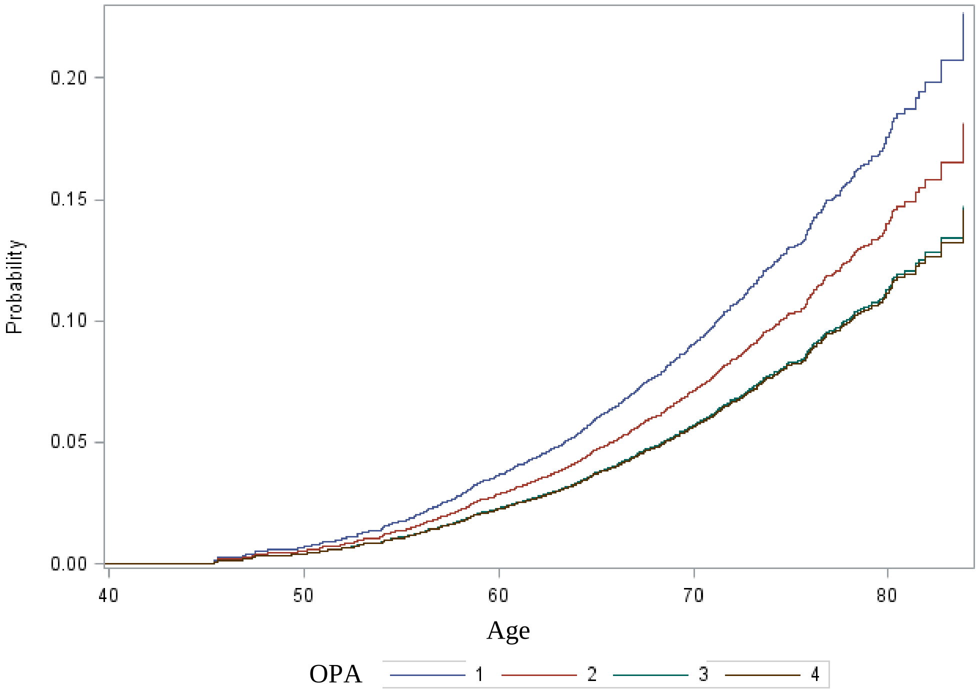
4.2. Summary of follow-up

In 15 years of follow-up, 580 nurses were hospitalized with IHD. These cases included 369 (63.6%) cases of angina pectoris, 138 (23.8%) cases of MI and 73 (12.6%) cases of other forms of IHD. Censoring at the date of death (from other causes of IHD at the hospital or of all-cause mortality out of hospital) or when emigrated occurred for 864 (7.1%) of the nurses. The number of person-years was 169,881 the median follow-up time was 14.8 years, ranging from 0.1 – 14.8 years and the average duration was 14.0 years. When the follow-up period was extended from 15 – 20 years, there were 869 nurses who had been hospitalized with IHD during the 20 year period, comprising 494 (56.9%) cases of angina pectoris, 232 (26.7%) cases of MI and 143 (16.4%) cases of other IHD. A total of 1469 (12.2%) died (from other causes of IHD at the hospital or of all-cause mortality out of hospital) or had emigrated. The number of person-years was 229,860 the average length of follow-up was 19.0 years and the median follow-up time was 20.6 years, ranging from 0.1 – 20.6 years.

4.3. The association between OPA and IHD – 15 and 20 years follow-up (Study I a)

The cumulative incidence curve in Fig. 6 shows the probability of experiencing an event of IHD at any given time during follow-up in each of the four OPA categories, in this case age, as age is the underlying time scale.

Fig. 6. Cumulative incidence curve, baseline in 1993 and 20 years follow-up. The probability of an event of ischeamic heart disease (IHD) at any given age



1=Strenuous OPA, 2=Demanding OPA, 3=Sedentary OPA, 4=Moderate OPA

The cumulative incidence curve shows that, over 20 years of follow-up, moderate and sedentary OPA are associated with the lowest probability of experiencing IHD at all ages, while it remains higher from demanding and strenuous OPA.

Both with 15 and 20 years' follow-up, high OPA (the collapsed categories strenuous and demanding) was associated with an increased risk of IHD in this cohort of Danish nurses. With 15 years of follow-up, the age-adjusted risk of IHD associated with high OPA was HR 1.42 (95% CI 1.17 – 1.72) and the fully adjusted HR was 1.34 (95% CI 1.08 – 1.66). With 20 years' follow-up, the age-adjusted HR for the association between high OPA and IHD was HR 1.31 (95% CI 1.13 – 1.53) and the fully adjusted HR was 1.24 (95% CI 1.05 – 1.46).

With 20 years' follow-up, a statistically significant association between OPA and risk of IHD both among nurses with demanding OPA and nurses with strenuous OPA was found compared to those with moderate OPA (Table 4). The risk of IHD increased with increasing level of OPA from the moderate OPA (the reference group) through demanding to strenuous OPA. Nurses with sedentary work had similar risk of IHD as those with moderate OPA. However, with 15 years' follow-up, a tendency of an increased risk of IHD was observed among nurses with sedentary OPA compared to those with moderate OPA, as shown in Table 2 in Article 1.

Table 4. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to physical activity at work (OPA) among 12,093 nurses participating in the Danish Nurse Cohort Study, 1993 – 2013. 869 cases of IHD.

		Basic model [a $]		Model 2		Model 3	
OPA	n/no with IHD	HR	95 % CI	HR	95 % CI	HR	95 % CI
Sedentary	2331/139	1.04	0.84 – 1,28	1.06	0.86 – 1.32	1.01	0.81 – 1.27
Moderate	4159/257	1	-	1	-	1	
Demanding	4965/407	1.27	1.08 – 1.48	1.26	1.07 – 1.48	1.22	1.03 – 1.45
Strenuous	638/66	1.66	1.27 – 2.18	1.51	1.12 – 2.02	1.41	1.04 – 1.92

Basic model: [§]Adjusted for age. [§§]Model 2: Adjusted for age and risk factors for IHD (family history of IHD, diabetes, BMI, smoking, alcohol consumption and LTPA. [§§]Model 3: Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking, alcohol consumption and LTPA), work pressure, influence at work, work hours and shift work.

4.4 Possible effect modification by LTPA (Study I b)

We investigated the possible effect modification by LTPA on the association between OPA and IHD in a Cox regression model. It was investigated both as the association between OPA and IHD stratified by level of LTPA and in a model with a common reference group, which was moderate

OPA and vigorous LTPA. This reference group was chosen because it was anticipated to be the combination with the lowest risk of IHD. There was a statistically significant multiplicative interaction between OPA and LTPA. The p-value of the age-adjusted interaction term was p=0.027 and in the fully adjusted model p=0.045 (Table 5).

Table 5. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to combined exposure to physical activity at work (OPA) and physical activity during leisure time (LTPA). This analysis was based on 12,008 female nurses from the Danish Nurse Cohort Study and 576 cases of IHD during follow-up 1993 – 2008 (85 nurses with missing information on LTPA)

			Common reference group for OPA and LTPA				Effect of OPA within strata of LTPA			
			Basic model 1§		Adjusted model 2§§		Basic model 1§		Adjusted model 2§§	
LTPA	**OPA**	No. of subjects/no. with IHD	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sedentary	Sedentary	195/14	3.31	1.73 – 6.35	2.81	1.41 – 5.57	2.12	0.89 – 5.06	1.94	0.77 – 4.87
Sedentary	Moderate	199/8	1.56	0.71 – 3.45	1.45	0.62 – 3.37	1	-	1	-
Sedentary	High	255/22	3.30	1.87 – 5.82	2.65	1.44 – 4.88	2.11	0.94 – 4.75	1.83	0.77 – 4.37
Moderate	Sedentary	1536/54	1.45	0.91 – 2.31	1.46	0.89 – 2.37	0.85	0.62 – 1.17	0.85	0.61 – 1.19
Moderate	Moderate	2871/125	1.70	1.11 – 2.59	1.71	1.10 – 2.66	1	-	1	-
Moderate	High	3662/214	2.15	1.43 – 3.22	2.09	1.36 – 3.21	1.26	1.01 – 1.58	1.22	0.96 – 1.55
Vigorous	Sedentary	583/28	2.02	1.28 – 3.76	2.17	1.25 – 3.79	2.20	1.29 – 3.76	2.17	1.25 – 3.79
Vigorous	Moderate	1063/26	1	-	1	-	1	-	1	-
Vigorous	High	1644/85	1.97	1.27 – 3.06	1.75	1.10 – 2.80	1.97	1.27 – 3.06	1.75	1.10 – 2.80

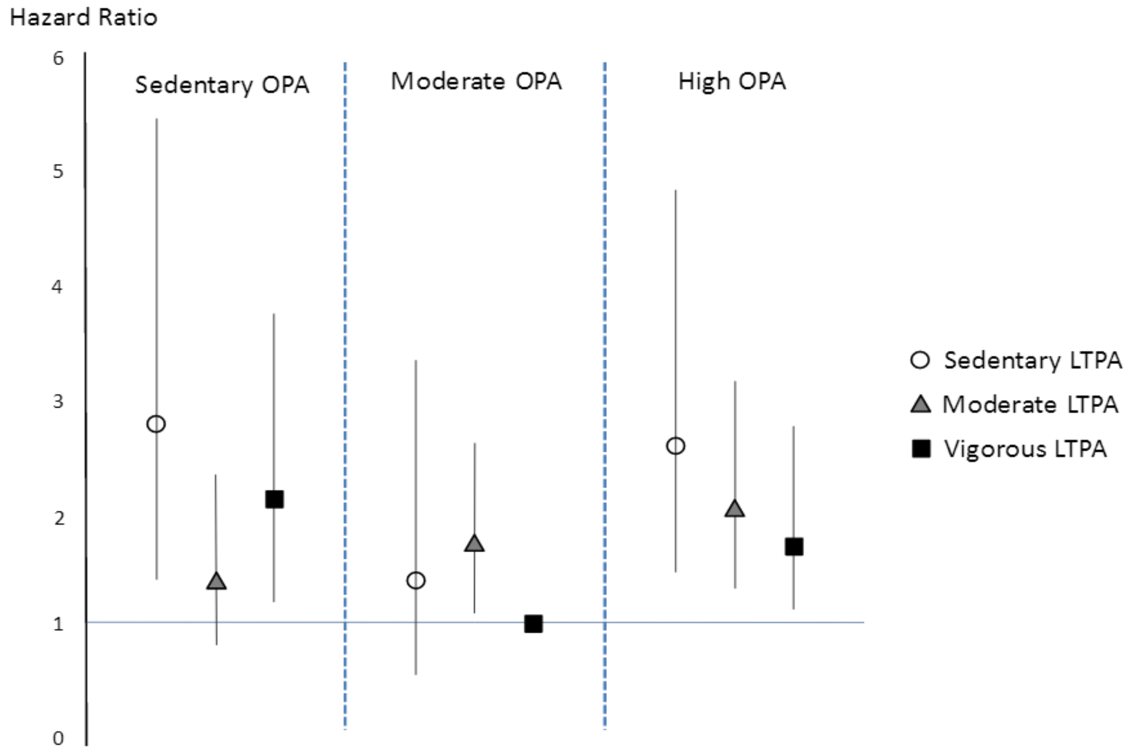
Measure of effect modification on multiplicative scale: OPA × LTPA: p=0.027 (Basic model 1§) and p= 0.045 (Adjusted model 2§).

§Basic model 1: Age as underlying timescale. §§Adjusted model 2: Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), work pressure, influence at work, work hours per week and shift work.

Both the analysis of the association between OPA and IHD stratified by level of LTPA, and the analysis with a common reference group showed that the association between OPA and IHD depended on the level of LTPA (Table 5). In the stratum of nurses with vigorous LTPA, a u-shaped association was observed with the lowest risk among nurses with moderate OPA. Among nurses with moderate LTPA, the risk of IHD was lowest among those with sedentary OPA and highest among those with high OPA. There were few nurses in the third stratum of nurses who were sedentary during leisure time, but a u-shaped association between OPA and IHD was indicated with the lowest risk of IHD among nurses with moderate OPA.

The analysis with a common reference group (nurses with moderate OPA and vigorous LTPA) revealed a similar pattern (Table 5). The result of this analysis is also illustrated in Fig. 7 where the risk of IHD among nurses with sedentary, moderate and high OPA respectively at different levels of LTPA is shown. The risk of IHD among nurses with high OPA was statistically significantly higher at all three levels of LTPA, compared to the reference group (moderate OPA and vigorous LTPA). However, the risk of IHD decreased with increasing level of LTPA – from 2.6 times higher among those with high OPA and who were sedentary during leisure time, to around two times higher among those with high OPA and moderate LTPA, and 75% higher among those with high OPA and vigorous LTPA. The risk of IHD in these three groups was, however, not statistically different because the CIs overlapped. Among nurses with moderate OPA, the lowest risk of IHD was also found among those with vigorous LTPA, but among nurses with sedentary OPA the lowest risk was found among those with moderate LTPA.

Fig. 7. Hazard ratio (HR) and 95% confidence interval (CI) for the combined exposure to physical activity at work (OPA) and physical activity during leisure time (LTPA) (compared to nurses with moderate OPA and vigorous LTPA). 12,008 female nurses from the Danish Nurse Cohort Study. 576 cases of IHD during follow-up 1993 – 2008.



Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), work pressure, influence at work, work hours per week and shift work.

Sensitivity analyses

Less severe cases of angina pectoris are treated in general practice and are thus not registered in the Danish National Patient Registry. To investigate whether this caused bias, a sensitivity analysis with all diagnoses of IHD excluding angina pectoris as outcome was performed. The fully adjusted HR for the association between high OPA and IHD, apart from angina pectoris, was HR 1.43 (95% CI 1.00-2.05), compared to nurses with moderate OPA, and thus slightly higher than the 34% increased risk of all forms of IHD from high OPA. The risk of IHD - excluding angina pectoris – among nurses with sedentary work was not different from the reference group as the fully adjusted HR was 0.97 (95% CI 0.59 – 1.59).

Self-rated health is a strong marker of health and associated with a number of health outcomes, including heart disease. Nurses with IHD at baseline were excluded, but a bad self-rated health could be a marker of subclinical IHD and thus a sensitivity analysis was performed investigating the association between high OPA and IHD among nurses with very good, good or moderate self-rated health. The risk of IHD among nurses with high OPA compared to those with moderate OPA in this subgroup of nurses was HR 1.31 (95% CI 1.05 – 1.63) and, thus, only slightly different from the 34% higher risk of IHD from high OPA in the whole study population.

4.5. Possible effect modification by hypertension (Study II)

Present or previous hypertension was reported by 1,400 (11.7%) of the nurses at baseline in 1993, and hereof 51.5% were treated with anti-hypertensive medication. There was no statistically significant difference in the distribution of OPA according to hypertension status (Table1, Article 2). The risk of IHD in hypertensive nurses was more than twice compared to the risk of IHD in normotensive nurses in the fully adjusted model (HR 2.12 (95% CI 1.72 – 2.61)).

Table 6 shows the results of an analysis of the association between OPA and IHD stratified by hypertension status and an analysis of the association between IHD and different combinations of level of OPA and hypertension status with a common reference group, which were normotensive nurses with moderate OPA.

The analysis with a common reference group (Table 6) showed that the risk of IHD among nurses with hypertension and high OPA was nearly three times higher than among nurses with normal blood pressure and moderate OPA. Nurses with normal blood pressure and high OPA had 21% higher risk of IHD, which was not statistically significant in the fully adjusted model (model 2 in Table 6). Also, hypertensive nurses with sedentary OPA had more than twice the risk of IHD of normotensive nurses with moderate OPA. The analysis of the association between OPA and IHD stratified by hypertension status showed a similar pattern of a strong association between high OPA and IHD among hypertensive nurses and a weaker association among normotensive nurses.

Table 6. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to the combined exposure to physical activity at work (OPA) and hypertension. 12,038 female nurses from the Danish Nurse Cohort Study. 576 cases of IHD during follow-up 1993 – 2008 (55 nurses had missing information on hypertension)

			Common reference group for OPA and hypertension status				Effect of OPA within strata of hypertension status			
			Basic model 1§		Adjusted model 2§§		Basic model 1§		Adjusted model 2§§	
	OPA	No. of subjects/no with IHD	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Normotensive	Sedentary	2054/71	1.06	0.79 – 1.42	1.04	0.77 – 1.42	1.06	0.79 – 1.42	1.04	0.77 – 1.42
Normotensive	Moderate	3691/130	1	-	1	-	1	-	1	-
Normotensive	High	4893/235	1.29	1.04 – 1.60	1.21	0.95 – 1.53	1.29	1.04 – 1.60	1.21	0.95 – 1.53
Hypertensive	Sedentary	269/25	2.57	1.67 – 3.94	2.33	1.48 – 3.67	1.47	0.86 – 2.50	1.49	0.85 – 2.64
Hypertensive	Moderate	455/30	1.75	1.17 – 2.60	1.56	1.01 – 2.39	1	-	1	-
Hypertensive	High	676/85	3.20	2.43 – 4.21	2.87	2.12 – 3.87	1.83	1.21 – 2.78	1.84	1.17 – 2.89

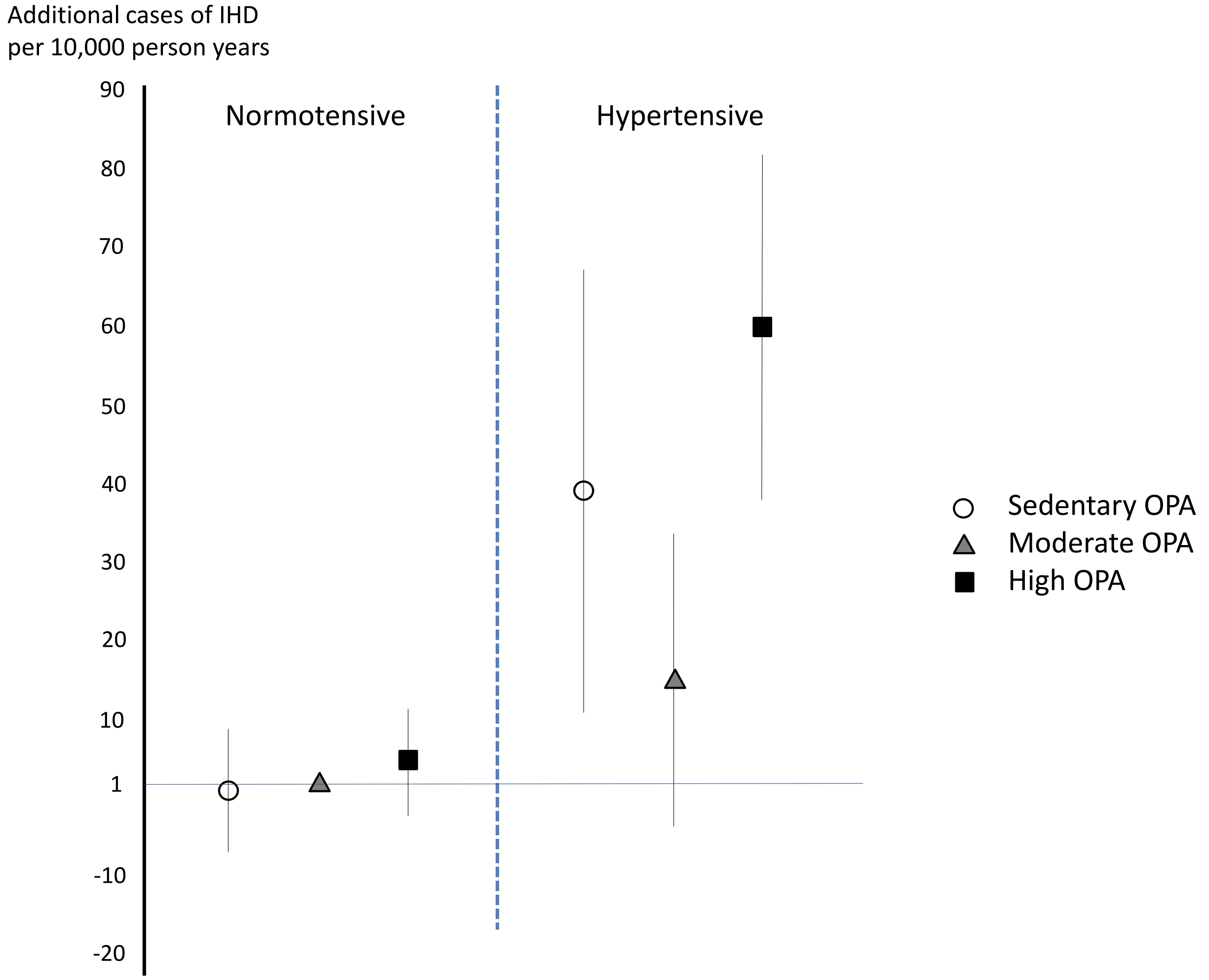
Measure of effect modification on multiplicative scale: OPA × hypertension included in the model: p= 0.328 (Basic model 1§§); p=0.249 (Adjusted model 2§§).

§Basic model 1: Age as underlying timescale. §§Adjusted model 2: Adjusted for age and risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), LTPA, influence at work, work pressure, work hours and shift work.

The analysis of the combined effect of OPA and hypertension (the results shown in Table 6) showed that there was no statistically significant multiplicative interaction between OPA and hypertension. However, statistically significant additive interaction between high OPA and hypertension measured as the relative excess risk due to additive interaction (RERI: 1.20 (95% CI 0.26-2.14)) was found in an analysis based on the same fully adjusted model.

This additive interaction was further investigated in an additive hazards model. The additive model showed an estimation of the additional numbers of cases of IHD per 10,000 person-years due to combined exposure to different combinations of levels of OPA and hypertension, compared to those with moderate OPA and normal blood pressure.

Fig. 8. Additive hazards model. Estimation of absolute size of the additional numbers of cases of incident ischaemic heart disease (IHD) due to the combined effect of hypertension and physical activity at work (OPA) (compared to normotensive nurses with moderate OPA) for 12,038 nurses from the Danish Nurse Cohort Study, 1993 – 2008.



Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), LTPA, work pressure, influence at work, work hours and shift work.

The result of the additive model, shown in Fig. 8 above and in Table 3 in Article 2 showed that there was statistically significant additive interaction between high OPA and hypertension (p=0.006). Among nurses with hypertension and high OPA, the numbers of additional cases of IHD were around three times higher than would be expected from adding the additional cases of IHD due to hypertension and high OPA together. This was illustrated by the finding of around five additional cases of heart disease due to high OPA and around 15 additional cases from hypertension (per 10,000 person-years) (Table 3, Article 2). While the sum of the two individual risk factors OPA and hypertension, in this case 20 extra cases, thus would be expected from the combination of hypertension and high OPA, the results showed that there were 60 additional cases among nurses with the combined exposure to hypertension and high OPA (Table 3, Article 2). Thus, there were 40 additional cases of IHD due to interaction between high OPA and hypertension.

The measure of additive interaction between sedentary OPA and hypertension was not statistically significant (p=0.174).

Sensitivity analysis: Adjustment for hypertension and hypertension medication

Because hypertension can also be a confounder, a sensitivity analysis was performed where the association between OPA and IHD was further adjusted for hypertension. In the fully adjusted model in Table 2 in Article 1, OPA was associated with 34% increased risk of IHD. Further inclusion of hypertension in this model slightly changed the estimate: (HR 1.32 (95% CI 1.07 to 1.64)).

Furthermore, a sensitivity analysis of the association between OPA and IHD was investigated among nurses with hypertension, stratified by use of anti-hypertensive medication, revealed that among those not using anti-hypertensive medication (n=654), the risk of IHD from high OPA was almost twice the risk than among those with moderate OPA but marginally significant in the fully adjusted analysis (HR 2.06 (95% CI 0.97 – 4.41)). Among nurses using anti-hypertensive medication (n=721), the risk of IHD from high OPA was somewhat lower (HR 1.87 (95% CI 1.02 – 3.44) – but still nearly 90% higher than among those with moderate OPA.

4.6. Possible effect modification by influence at work (Study III)

The association between influence at work and risk of IHD

Table 7 shows the association between influence at work and risk of IHD with 20 years follow-up. Having some or very low influence at work did not increase the risk of IHD, compared to having high influence at work. A tendency of an increased risk of IHD among nurses with no influence at work was observed. However, this was not statistically significant and this group of nurses was very small.

Table 7. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to influence at work among 12,093 nurses participating in the Danish Nurse Cohort Study 1993 – 2013. 869 cases of IHD during follow-up

		Basic model 1		Adjusted model 2	
Influence at work	No. of subjects/no. with IHD	HR	95 % CI	HR	95 % CI
High	4476/322	1		1	
Some	6051/457	1.04	0.90 – 1,20	0.99	0.84 – 1.15
Very low	1072/70	0.92	0.71 – 1.19	0.89	0.67 – 1.18
None	194/20	1.50	0.96 – 2.35	1.31	0.80 – 2.13

§Basic model 1: Age as underlying timescale. §§Adjusted model 2: Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), LTPA, work pressure, work hours and shift work.

The association between combinations of OPA and influence at work and the risk of IHD; the possible effect modification by influence at work

In Table 8, an analysis of the association between joint exposure to OPA and influence at work and risk of IHD with a common reference group is shown. The reference group was nurses with moderate OPA and high influence at work and the age-adjusted and fully adjusted HRs compared to this group for the other seven combinations of OPA and influence at work are presented. Furthermore, Table 8 shows the association between OPA and risk of IHD within strata of high or low influence at work.

Table 8. Hazard ration (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to combined exposure to physical activity at work (OPA) and influence at work for 12,093 female nurses from the Danish Nurse Cohort Study. 869 cases of IHD during follow-up 1993 – 2013.

			Common reference group for OPA and influence at work				Effect of OPA within strata of influence at work			
			Basic model 1[§]		Adjusted model 2[§§]		Basic model 1[§]		Adjusted model 2[§§]	
Influence at work	**OPA**	No. of subjects/no. with IHD	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
High	Sedentary	1481/81	0.87	0.65 – 1.16	0.87	0.64 – 1.17	0.87	0.65 – 1.16	0.87	0.64 – 1.17
High	Moderate	1598/106	1		1		1		1	
High	Demanding	1544/124	1.18	0.91 – 1.53	1.13	0.86 – 1.49	1.18	0.91 – 1.53	1.13	0.86 – 1.49
High	Strenous	153/11	1.07	0.57 – 1.99	1.10	0.59 – 2.06	1.07	0.57 – 1.99	1.10	0.59 – 2.06
Low	Sedentary	850/58	1.06	0.77 – 1.47	1.06	0.77 – 1.48	1.25	0.93 – 1.70	1.24	0.91 – 1.70
Low	Moderate	2561/151	0.85	0.66 – 1.09	0.85	0.66 – 1.11	1		1	
Low	Demanding	3421/283	1.13	0.91 – 1.42	1.14	0.90 – 1.46	1.33	1.09 – 1.63	1.34	1.08 – 1.66
Low	Strenuos	485/55	1.64	1.18 – 2.27	1.46	1.02 – 2.09	1.93	1.42 – 2.62	1.71	1.22 – 2.40

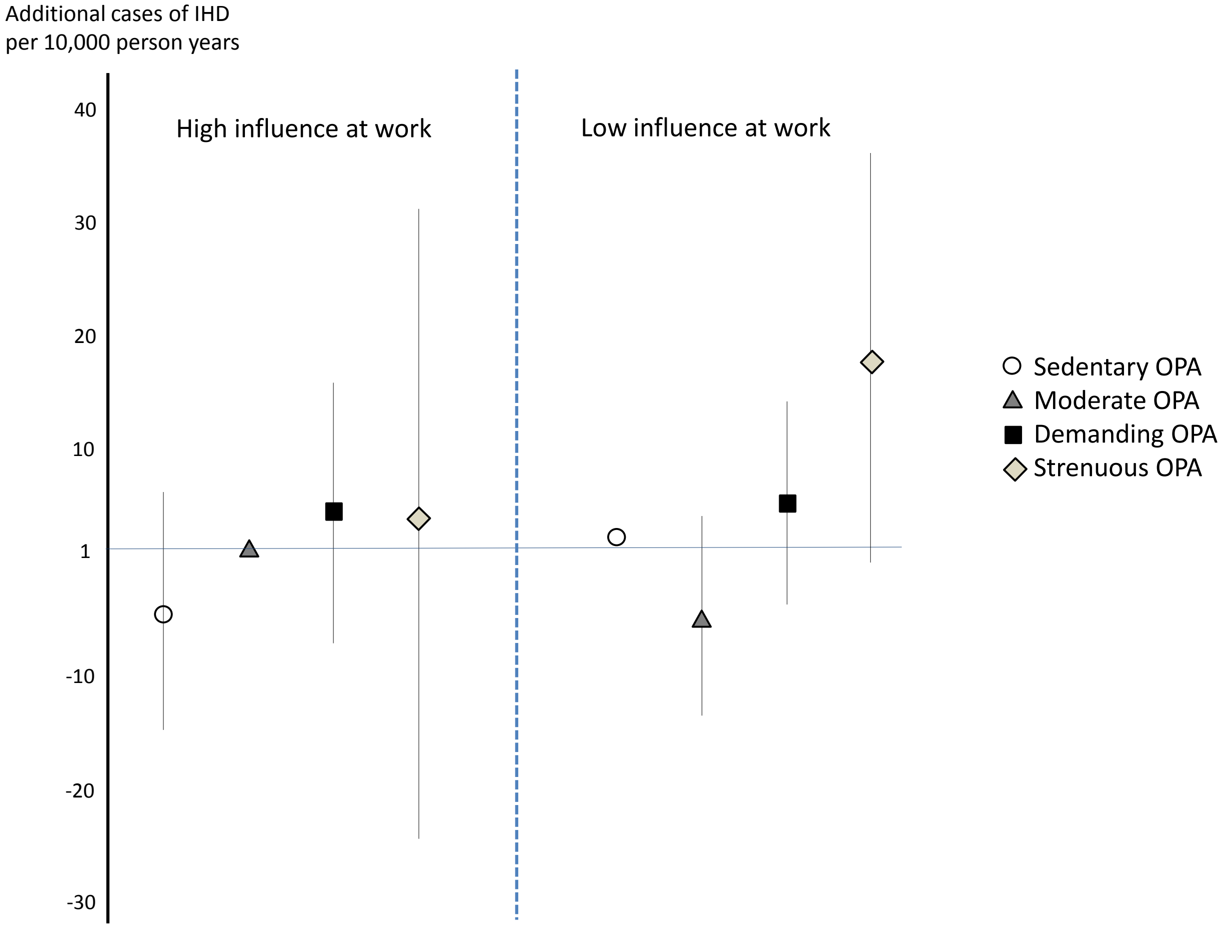
Measure of effect modification on a multiplicative scale: OPA × influence at work included in the model: p=0.184 (Basic age adjusted model) and p=0.297 (Adjusted model 2).

[§]*Basic model 1: Age as underlying timescale.* [§§]*Adjusted model 2: Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), LTPA, work hours and shift work.*

The analysis of the association between different combinations of OPA and influence at work with a common reference group showed that nurses with strenuous OPA and low influence at work had 46% higher risk of IHD compared to nurses with moderate OPA and high influence at work. This difference was statistically significant. Those with strenuous OPA and high influence at work did not have higher risk of IHD than the reference group (Table 8). The stratified analysis showed a similar tendency of an increased risk of IHD from strenuous work among nurses with low influence at work, but not among those with high influence at work (Table 8).
Compared to nurses with moderate OPA and high influence at work, the risk of IHD from demanding OPA did not differ between nurses with low influence at work and nurses with high influence at work in the analysis with a common reference group.

The test for multiplicative interaction between OPA and influence at work was not statistically significant, meaning that, on the multiplicative scale, a modifying effect of influence at work was not found (Table 8). The results from the multiplicative model in table 8, however, did indicate that the risk of IHD from strenuous OPA was different depending on the level of influence at work. An additive hazards model was used to further investigate whether this difference was due to an adverse additive interaction between strenuous OPA and low influence at work and to explore the absolute effects of different combinations of OPA and influence at work on the risk of IHD (Fig. 9 and Table 4 in Article 3). In this model, the association between different combinations of OPA and influence at work and absolute risk of IHD were calculated as the number of additional cases of IHD per 10,000 person-years. The reference category was nurses with moderate OPA and high influence at work. The results from the fully adjusted analysis are shown in Fig. 9

Fig. 9. Additive hazards model. Estimation of absolute size of the additional numbers of cases of incident ischaemic heart disease (IHD) due to the combined effect of physical activity at work (OPA) and influence at work (compared to nurses with moderate OPA and high influence at work) for 12,093 nurses from the Danish Nurse Cohort Study, 1993 – 2013.



Adjusted for age, risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), LTPA, work hours and shift work.

In the fully adjusted analysis, there were 18 additional cases of IHD per 10,000 person-years among nurses with strenuous OPA and low influence at work compared to the reference group. Among nurses with strenuous OPA and high influence at work, there were 4 additional cases of IHD of additional cases of IHD (Fig. 9).
The p-value for the additive interaction between strenuous OPA and influence at work was not statistically significant, but with a p-value of 0.065 in the age-adjusted analysis there was a tendency of an additive interaction. In the age-adjusted analysis (the results are shown in Table 4 in Article 3), this additive interaction could explain 26.8 additional cases of IHD per 10,000 person years (26.8 (95% CI -1.6 – 55.3).
There were, however, rather few nurses reporting strenuous work and even fewer when divided into high and low influence at work, respectively. The CIs of the HRs of the groups with strenuous OPA and respectively high and low influence at work overlapped.

The absolute risk of IHD from demanding OPA did not differ significantly according to the level of influence at work as shown in figure 9. Compared to the reference group, nurses with demanding OPA and high influence at work had 4.6 and those with demanding OPA and low influence at work had 5.2 additional cases of IHD per 10,000 person years in the fully adjusted analysis (Fig.9).
Among nurses with sedentary OPA, there were 4.6 fewer cases of IHD among those with high influence at work and among nurses with sedentary OPA and low influence at work there were 2.2 additional cases of IHD per 10,000 person-years.

Sensitivity analyses

Because both work pressure and influence at work ($p<0.001$) and work pressure and OPA ($p<0.001$) are correlated, work pressure was not included in the fully adjusted analyses. Additional adjustment for work pressure was investigated in a separate analysis – corresponding to model 2 in Table 9 but with further adjustment for work pressure. This further adjustment slightly attenuated the associations and did not change their direction (data not shown). Furthermore, the possible three-way interaction between work pressure, OPA and influence at work was investigated, but the age-adjusted p-value for the interaction term between OPA, influence at work and work pressure was $p=0.974$ and thus no tendency for an interaction was found.

The follow-up time was 20 years in the investigation of possible effect modification of the association between OPA and IHD by influence at work, and as the nurses were 45 – 64 at baseline in 1993 many of them had retired at the end of follow-up. Therefore, the age-adjusted association between OPA, influence at work and IHD was investigated in an additional sensitivity analysis where the nurses were censored when they became 70 years. This revealed a stronger association between risk of IHD and strenuous (HR 1.79 (95% CI 1.29 – 2.47)) and demanding (HR 1.42 (95% CI 1.18 – 1.71)) OPA than in the main analysis (as seen in Table 4). Furthermore, investigating the association between influence at work and risk of IHD in a comparable model revealed that having no influence at work was associated with a significantly higher risk of IHD (HR 1.81 (95% CI 1.09 – 3.00)).

4.7. Additional analyses

4.7.1. Analysis of exposure change in OPA between 1993 and 1999 (additional analysis I)

With a rather long follow-up time and measurement of exposure at one point in time only, there will inevitably be some degree of misclassification due to changes in exposure level during follow-up. To gain insight into the extent to which exposure to OPA changes in the study population, the exposure to OPA among those answering the OPA question both in 1999 and 1993 was investigated. Table 9 shows the distribution of exposure to OPA in 1993 according to the level of OPA in 1999. Nearly two-thirds of the nurses reporting being mainly sedentary at work in 1999 had the same exposure in 1993 and 87.4% had either sedentary or moderate OPA in 1993. A much smaller proportion of the nurses with strenuous OPA in 1999 had the same exposure in 1993, but 77.3% had either demanding or strenuous OPA in 1993. Nearly wo-thirds of the nurses with demanding OPA in 1999 also had demanding OPA in 1993 and 77.9% had either demanding or strenuous OPA. Among those with demanding OPA in 1999, 23.6% had moderate OPA in 1993 and among those with strenuous OPA in 1999, 18.2% had moderate OPA in 1993. Among nurses with moderate OPA in 1999, nearly 60% had the same exposure in 1993, but nearly 25% had demanding OPA in 1993.

Table 9. Distribution of physical activity at work (OPA) exposure in 1993 among 7,029 nurses from the study population answering the OPA question in the 1999 study (percentage)

	OPA in 1993	**Sedentary**	**Moderate**	**Demanding**	**Strenuous**	Total
OPA in 1999						
Sedentary		64.3	23.1	11.0	1.6	1567
Moderate		14.3	58.8	24.5	2.4	2520
Demanding		5.1	23.6	64.6	6.7	2683
Strenuous		4.6	18.2	51.0	26.2	259
Total		1518	2523	2655	333	7029

4.7.2. Analysis of the OPA-IHD association among nurses with the same exposure in the 1993 and 1999 surveys (additional analysis II)

A separate analysis among nurses participating in and with the same exposure to OPA (in the categories: sedentary, moderate and high (demanding/strenuous) OPA) in both the 1993 and 1999 survey was performed. This analysis showed that those with strenuous OPA in 1993 and who were still exposed to demanding or strenuous OPA in 1999 had a more than double as high risk of IHD as those with moderate OPA at both surveys (Table 10). Table 10 also shows that those with demanding OPA had a smaller and not significantly increased risk of IHD but an association of approximately same size as among those with demanding OPA at baseline in the analysis among all 12,093 nurses, as shown in Table 4.

Table 10. Hazard ratio (HR) for ischaemic heart disease (IHD) according to physical activity at work (OPA) among 4626 nurses participating in the Danish Nurse Cohort Study 1993 and 1999 with the same exposure level (in the categories: high, moderate and sedentary OPA); 263 cases of IHD

		Basic model 1§	
OPA in 1993	No. of subjects/no. with IHD	HR	95 % CI
Moderate	1488/73	1	-
Sedentary	1012/50	1.07	0.74 – 1.53
Demanding	1874/113	1.20	0.89 – 1.61
Strenuous	252/27	2.25	1.45 – 3.50

§*Model 1 age as underlying time scale*

4.7.3. Adjustment for civil status (additional analysis III)

A question about household income was not included in the 1993 questionnaire, but was included in the 1999 survey. There was a statistically significant association between household income and civil status in an analysis based on data from the 1999 survey ($p < 0.001$). Whereas more than 90% of the nurses with household incomes above DKK 400,000 per year were married or living with a partner, only 25% of the nurses with the lowest income (< DKK 199,000 per year) were married or living with a partner. Civil status was measured in 1993 and further adjustment for civil status in in an analysis otherwise similar to the fully adjusted model 2 in Table 4 showed a nearly similar result for the association between high OPA and risk of IHD as in Table 2 (data not shown).

5. DISCUSSION

The overall aim of the present thesis was to investigate the association between OPA and risk of IHD and, specifically, whether high OPA is a risk factor for developing IHD and whether being physically active during leisure time or having high influence at work could counteract a detrimental association between high OPA and IHD. Furthermore, the aim was to investigate whether individuals with hypertension were at particular risk of IHD from high OPA. In the discussion, the main findings will be discussed and interpreted. Furthermore, the methodological strengths and limitations of the study will be discussed.

5.1 Main findings

- High physical activity at work was associated with increased risk of IHD. Based on 20 years follow-up, a graded increase in the risk of IHD from moderate through demanding to strenuous OPA was indicated.

- LTPA modified the association between OPA and IHD. A trend of lower risk of IHD from high OPA with increasing level of LTPA was observed. However even vigorous LTPA did not completely counteract the increased risk of IHD associated with high OPA.

- Hypertensive nurses with high OPA had a nearly three times higher risk of IHD than normotensive nurses with moderate OPA. Among normotensive nurses, high OPA was associated with a much lower risk of IHD. More than half of the additional cases of IHD due to the combined exposure to high OPA and hypertension were explained by an additive interaction between high OPA and hypertension. This strongly indicates that high OPA is a particular risk factor for IHD among hypertensive women.

- A modifying effect of influence at work on the association between strenuous OPA and risk of IHD was observed. Strenuous OPA in combination with low influence at work was associated with a higher risk of IHD, which was not found in combination with high influence at work. This finding suggests that high influence at work could potentially counteract the enhanced risk of IHD among women with strenuous OPA.

5.2 The association between OPA and IHD

High OPA as risk factor for IHD – interpretation in relation to existing knowledge

This study showed that high OPA was associated with increased risk of IHD and the first hypothesis of Study I was thus confirmed. A sensitivity analysis among nurses who had the same OPA exposure in 1993 and 1999 confirmed the result. Furthermore, a graded increase in the risk of

IHD was observed from moderate OPA through demanding to strenuous OPA in Study III, where the follow-up time was 20 years. Also, supporting the finding that high OPA could be a risk factor for IHD is the fact that confounding due to socioeconomic factors is diminished in this study. To my knowledge, it is the only study that shows the relation between OPA and cardiovascular health in a single profession of women, who, furthermore, have the same educational background. To a large extent, this avoids the difficulty of disentangling the effect of OPA from the effect of socioeconomic factors, an issue in studies that involve several professions and social classes [82].

The present study is one of very few studies among women that have shown that high OPA could be a risk factor for IHD. However, two former cohort studies have shown similar results among women. One of them was a general population study that showed an age-adjusted increased risk of IHD from high OPA among women [73]. Yet, a Taiwanese study that also included different occupations showed a tendency for a higher risk for CVD among women with a high level of OPA, compared to those with a low level of OPA. That study, however, had a small sample size of women and the low power of the study might explain why a significant association was not found [74]. Also in agreement with the finding of the present study is a case control study from 2004 that showed a tendency towards an increased risk of MI from strenuous work and an increased risk of MI from repetitive lifting and heavy lifting at work among women [160]. In accordance with the finding in the present study, there are also a number of studies among men that have shown a detrimental association between high OPA and an increased risk of IHD [34;35;80], MI [33;81] or CVD [74;82], especially in more recent studies.

There are, however, also contrasting findings. Some of the previous studies including women have shown no association between high OPA and IHD, MI or CVD [33;77-79] or a protective effect of high OPA in relation to IHD or MI [15;75;76] among female workers. Different assessment of OPA could account for some of the different findings, e.g., whether a single question is used – as in the present study – or whether composite measures of OPA from more questions [74;79;92] or from information from two surveys are used [33]. Furthermore, a number of different questionnaires and categorisations of OPA have been used. More uniform ways of measuring OPA in future studies would improve our ability to compare the results between studies.

Another possible explanation for the discrepancy between the finding of a detrimental effect of high OPA in the present study and no – or only an indication of – an association between high OPA and risk of IHD among women in some of the previous studies could be differences in the statistical power between studies. IHD on average occurs later in life among women than among men [47;161] and is thus less prevalent in women of working age. Therefore, in studies among female workers, large study populations and a rather long follow-up time might be required to detect associations of a size similar to the 30% increased risk of IHD from high OPA shown in the present study. The age groups included in a study will, furthermore, affect the numbers of cases of IHD during follow-up. The study population in the present study is larger than many of the previous studies among women, the nurses were middle-aged at baseline and the follow-up was rather long. This will lead to a higher number of cases of IHD during follow-up and an improvement in the power of the study and differences in the size and age-composition of the study populations and length of follow-up could, thus, partly explain the different findings.

It is, however, noteworthy that two former studies – both based on a large population of women and with a long follow-up time – found a protective effect of high OPA in relation to risk of CVD [75;76]. The two studies also resembled the present study in that the assessment of OPA was based on a single question, similar to the OPA question in the present study. In contrast, however, these two previous studies also included younger age groups than in the present study. The health impact of high OPA could differ between age-groups, e.g., due to differences in physical capacity [69;162;163]. This was suggested in a recent study from Sweden [164] that analysed men and women together. This study showed that, in contrast to the middle-aged workers, the group of younger workers had lower risk of MI from high OPA involving lifting or carrying, and it was discussed whether this could be explained by higher cardiorespiratory capacity among the younger workers [164]. In line with this finding, the lowest risk of all-cause mortality from high OPA was found among female workers 17 – 39 years in another recent study [93]. This difference between age groups could be one possible explanation of the difference in the finding in the present study and the previous two cohort studies in finding a protective effect of high OPA on CVD.

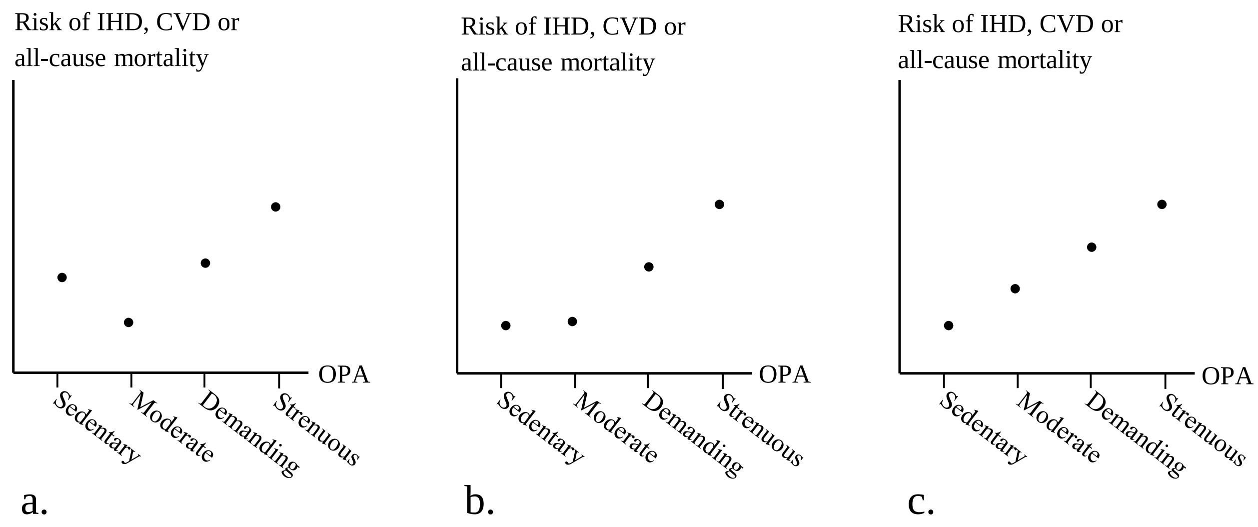
As discussed above, there could be a number of factors that might lead to different findings between studies. As the present study population only comprised nurses, there is, however, also the possibility that special working conditions among nurses might partly explain the findings. However, the finding of a higher risk of IHD among nurses with high OPA is in accordance with findings from three studies among women and a number of recent studies among men, all based on general populations, and, thus, a number of different occupations; this could suggest that high OPA is also risk factor for IHD in broader populations of workers.

Sedentary and moderate OPA and risk of IHD

While long periods of sitting during leisure time have been suggested to be independently associated with increased risk of all-cause mortality [140] and CVD [139], the existence of a detrimental association between sedentary work and risk of CVD and mortality remains controversial [141;165;166]. In the present study with 15 years follow-up, there was an increased risk of IHD from both sedentary OPA and high OPA compared to moderate OPA and thus a u-shaped association as illustrated in Fig. 10.a. was observed. In line with this finding, a u-shaped association was indicated among women in two other Danish studies [33;92].

In Study III, with 20 years follow-up, the risk of IHD among nurses with sedentary OPA did not, however, differ from the risk of IHD among those with moderate OPA (Fig. 10.b.). Due to the longer follow-up time, more nurses could have retired or changed exposure and this might have led to dilution of the rather small size of the increased risk of IHD from sedentary OPA that was observed with 15 years follow-up. Alternatively, the indication of an increased risk of IHD from sedentary OPA with 15 years follow-up could be a spurious finding.

Fig. 10. Schematized illustration of different shapes of the association between OPA and detrimental health outcomes as IHD, CVD and all-cause mortality observed in the present and former studies.



In contrast to the finding in the present study – that moderate OPA is associated with a lower risk of IHD or a risk similar to that from sedentary OPA – a number of studies among men have shown that both moderate, demanding and strenuous OPA is associated with an increased risk of IHD or all-cause mortality, compared to sedentary OPA [32;33;33;34]. This is illustrated in Fig. 10.c. In these studies the moderate OPA category comprised primarily standing and walking at work and, thus, was similar to the moderate OPA category in the present study. Standing for many hours each working day could impose strain on the cardiovascular system, caused by venous pooling in the legs and increased blood pressure, which, over time, could lead to varicose veins and progression in atherosclerosis [64;65]. In contrast, walking, which facilitates circulation, is dynamic and involves varying muscle groups, which could be health-promoting in the right dose. Patterns of physical activity might be an important parameter in determining whether OPA is beneficial or detrimental. It could be that, among nurses, the pattern of physical activity in the moderate OPA category in the present study is actually health-promoting by constituting primarily walking interspersed with small breaks of sitting. Actually, in a study from 2002 among Danish nurses, 68% of the nurses reported that they seldom or never had to stand for prolonged periods at work [72]. In other professions, the category of mainly standing or walking OPA could generally be detrimental, e.g., standing through a full working day.

It is not yet established whether being mainly sedentary at work imposes a risk in relation to cardiovascular health, as indicated in the present study with 15 years follow-up, and whether this might also be the case for moderate OPA in certain occupations. The low risk of IHD among nurses with moderate OPA in the present study could be due to special working conditions and a pattern of physical activity among nurses with moderate OPA that might be health-promoting.

The contrasting effects of OPA and LTPA on risk of IHD

In the present study, being sedentary during leisure time was associated with a 50% higher risk of IHD, compared to being engaged in vigorous LTPA. This is in line with findings from previous studies of a beneficial effect of LTPA on cardiovascular health [28;109]. The finding in the present study – of an inverse association of OPA and LTPA in relation to risk of IHD – confirms the findings of former studies of an inverse health effect of physical activity at work and during leisure time, which has been called a "health paradox" [22;167]. There have been different hypotheses in the attempt to explain the opposing health effects of high physical activity at work and during leisure time, as outlined in the Background section (2.2). Studies such as the present study, in which crude measures of OPA and LTPA are applied, are, however, not suited to an examination of which differences between OPA and LTPA might be responsible for the contrasting health effects. The hypotheses about the different health effects of OPA and LTPA should be specifically addressed in future studies that would be designed to disentangle the aspects of OPA and LTPA that are responsible for the differences in the health effects of OPA and LTPA.

5.4 Modifying effect of LTPA

It was one of the hypotheses of the present study that vigorous LTPA could modify and thus counteract an increased risk of IHD associated with high OPA. The results of Study I b showed that the association between OPA and IHD varied by level of LTPA. In accordance with the hypothesis in Study I b, a protective effect of being physically active during leisure time among those with high OPA was indicated. However, even being engaged in vigorous physical active during leisure time did not completely eliminate the increased IHD risk.

A possible modifying effect of LTPA on the association between OPA and IHD has been investigated in a number of recent studies, of which only two included women. In contrast to the findings in the present study, a Finnish study found a decreased risk of IHD among women with moderate/high OPA in all combinations with LTPA and active commuting and with the lowest risk of IHD among women with moderate/high LTPA and high OPA [75]. Yet another study showed no increased risk of either MI or all-cause mortality from high OPA in either level of LTPA [33].

In accordance with the present study, a number of studies among men have shown or indicated the existence of a protective effect of a high level of LTPA or high cardiorespiratory fitness with respect to heart disease or all-cause mortality from high OPA [33;34;80;82;114]. In some of these studies, a high level of LTPA or cardiorespiratory fitness completely counteracted the increased risk of IHD or all-cause mortality from high OPA [33;34]. This is in contrast with the finding in the present study that showed that, even among nurses with vigorous LTPA, there is still a significantly increased risk of IHD from high OPA. This finding is corroborated by a study by Clays et al., who showed a doubled risk of all-cause mortality among men with high OPA and low LTPA, but also an 83% increased risk among men with high OPA and a high level of LTPA [96]. In another cohort of men from Belgium, the authors even found the highest risk of IHD among those with high OPA and moderate to high LTPA [35]. The interplay, though, seems to be complex, and it is possible that some workers with the highest physical work demands might be in need of recovery, rather than additional physical activity, as discussed by Clays [35] and Krause [81].

A recent Danish cohort study, however, concluded that all levels of LTPA were beneficial for both male and female workers, irrespective of their level of OPA [168]. Overall, recent evidence of the interplay between OPA and LTPA or fitness and risk of CVD and all-cause mortality supports the indicated beneficial effect in the present study of a high level of physical activity during leisure time for those with high OPA.

5.4 Modifying effect of hypertension

In the conceptual model outlined in the introduction to the present thesis, it is suggested, that hypertension could exacerbate the detrimental effects of high OPA, leading to increased risk of IHD. However, it is not known whether hypertensive workers with high OPA are particularly at risk of heart disease. Therefore, one of the objectives of this study was to investigate whether hypertension modifies the association between high OPA and risk of IHD. The hypothesis in Study II was that the risk of IHD from high OPA is higher among women with hypertension than among normotensive women. This was confirmed as the analysis of the combined exposure to OPA and hypertension and risk of IHD showed that the HR for IHD was nearly three times higher among nurses with high OPA and hypertension compared to those with moderate OPA and normal blood pressure. Furthermore, an additive interaction explained 40 out of 60 additional cases of IHD per 10,000 person-years among hypertensive nurses exposed to high OPA, compared to normotensive nurses with moderate OPA. This means that, when exposed to both hypertension and high OPA, there is an enhanced risk of IHD that exceeds the individual effects of high OPA and hypertension. This finding indicates that hypertensive nurses might be at excessive risk of IHD from high OPA. Changing the working conditions selectively for those with hypertension from high to moderate OPA could, therefore, have higher preventive effect on IHD than would be expected from the association between high OPA and IHD among all nurses.

To my knowledge, only very few studies have investigated whether hypertensive individuals are particularly vulnerable to exposure to high OPA in relation to cardiovascular health and all of these are among men. In accordance with the finding of the present study, a Finnish study found a higher risk of IHD from high physical workload among men with hypertension at baseline, compared to those who were normotensive at baseline with no exposure to physical workload, whereas normotensive men with high physical workload did not have higher risk of IHD [37]. In contrast, a Danish study among middle-aged men showed that high OPA was associated with similar risk of IHD among hypertensive and normotensive men, but when social class was included in a fully adjusted model, an increased risk of IHD from high OPA was seen only among normotensive men [38].

It is not known which aspects of high OPA might be responsible for an excess risk of IHD among hypertensive individuals. A study from Belgium indicated that mainly static work could be associated with higher blood pressure, at work, during leisure time and during sleep, in that this association was only found using a self-reported measure but not using objective measures, disregarding static work [39]. In the OPA question in the present study, it is mainly work including lifting and carrying tasks and physically exerting work that separates the two high OPA categories from the moderate OPA category, and it could be that the combination of hypertension with static work is an important issue to consider [39].

A prospective study among middle-aged men found a significant increase in systolic blood pressure among workers with high physical workload [37], and this finding could indicate that increased blood pressure could be in the causal pathway between high OPA and IHD. In the present study, a sensitivity analysis showed that adjustment for hypertension at baseline only slightly changed the estimate of the association between high OPA and IHD. If hypertension was an intermediate variable, an attenuation of the association would have been expected [114 169] and, thus, there was no indication of an intermediate role of hypertension. Rather, the present study indicates a role of hypertension as an effect modifier of the association between high OPA and IHD.

The finding in this cohort – that women with hypertension could be at considerably higher risk of IHD from high OPA than normotensive women – is a significant result. It is, to my knowledge, the first study among women to show this.

5.5 Modifying effect of influence at work

One of the objectives of the present study was to investigate whether the adverse association between high OPA – analysed as demanding and strenuous OPA separately – and risk of IHD could be modified and, thus, reduced by having high influence at work. Strenuous OPA was associated with a higher risk of IHD in combination with low influence at work, but this detrimental association was not found in combination with high influence at work. A possibly protective effect of high influence at work in relation to the association between strenuous OPA and risk of IHD was also found in the additive model and there was a tendency of an additive interaction between strenuous OPA and influence at work. The results of the present study therefore indicated that the association between strenuous OPA and IHD could be modified and thus depend on the level of influence at work. The detrimental additive interaction between strenuous OPA and influence at work, that was indicated, explained the additional cases of IHD among nurses with strenuous OPA and low influence at work and this suggests that this group may be particular risk of IHD. That the additive interaction between strenuous OPA and influence at work was only marginally statistically significant could be influenced by the limited statistical power due to a relatively low number of nurses in the strata with strenuous OPA and high or low influence at work, respectively.

In contrast to the association between strenuous OPA and risk of IHD, the association between demanding OPA and risk of IHD did not differ according to level of influence at work. It could be that influence on the organisation of the daily work mainly influences risk of IHD from high OPA in the most strenuous jobs.

In contrast to the finding in the present study – of a possible modifying effect of influence at work – a recent study from Belgium among middle-aged men showed no indication of a modifying effect of job control on the association between physical work demands and risk of IHD [40]. Different assessment of OPA and influence at work could be one explanation for the different findings. In the present study, influence at work modified the association between IHD and strenuous but not demanding OPA. In the Belgian study, a continuous OPA measure was constructed from five questions and dichotomized, and perhaps this did not allow for an exploration of the combined effect of the most strenuous level of OPA and job control. Furthermore, job control was measured by means of the Job Content Questionnaire by Karasek et al. [40;120], which includes a number of questions about both skill discretion and decision authority. It thus offers an index of more aspects of job control than the single question in the present study, which only concerns one of the aspects of decision authority. It might be that not all aspects of job control are equally important for counteracting the adverse effect of high OPA. In this regard, the ability to plan and organise one's work tasks could be, for example, more important in counteracting a detrimental effect of physically strenuous work on heart health than the level of skill and creativity that is required on the job. In the study from Belgium, the separate sub-dimension of job control, decision authority, did, however, not modify the association between physical demands at work and risk of IHD.

Apart from the Belgian study, only one previous study was identified that investigated the health effect of combined exposure to physical and psychosocial factors. This study from 1985 investigated the combined effect of hectic work and heavy lifting in relation to risk MI [131]. More studies examining the potential buffering effect of psychosocial work factors on the association between OPA and cardiovascular health are needed. Future studies in populations where more participants are exposed to strenuous work and with better exposure contrast regarding influence at work must show whether the finding of the present study can be confirmed.

The opportunity to organise and plan work tasks and thus e.g. to be able to take a rest between strenuous tasks at work could influence whether strenuous work has detrimental health effects for the individual. The finding that nurses with strenuous OPA had an increased risk of IHD in combination with low influence at work that was not found in combination with high influence at work suggests that influence at work could be an important factor to consider among workers with strenuous OPA and that a higher level of influence at work in this group of workers could potentially contribute to the prevention of IHD.

5.6 Methodological considerations

A great advantage of the present study is that it comprises a large cohort of women. This made it possible to conduct stratified analyses and, in some of the analyses, to detect statistically significant interactions. Another major strength of the study is the high response rate at baseline in 1993, together with the fact that the study was based on almost the entire target population – and was thus representative – of female Danish nurses, both of which facts lower the risk of selection bias.

One of the underlying hypotheses of the present study was that the causal pathway from high OPA to IHD may be through atherosclerosis. Therefore, it is a strength of the study that the outcome is directly related to and caused by atherosclerosis. Using registry-based information about incident IHD provides valid information on incident IHD that is independent of information about exposure and provides information on IHD before baseline. Furthermore, there was almost no dropout/loss at follow-up.

The follow-up time was relatively long and, in a population aged 45 – 64 years and 15 – 20 years' follow-up, many of the participants will retire during follow-up and are no longer exposed to OPA. A sensitivity analysis where the participants were censored at age 70, if not previously censored, showed, however, an even stronger association between risk of IHD and both demanding and strenuous OPA. This indicated that possible bias from an increasing number of nurses no longer exposed to occupational factors due to retirement did not explain the association between high OPA and IHD, but attenuated the extent of the association. However, if more nurses with high OPA left work or retired earlier than nurses with sedentary or moderate OPA, it could bias the results, due to different lengths of exposure at different levels of OPA. A study based on the 1993 Danish Nurse Cohort Study among nurses 51 – 59 years old, however, showed that high physical demands at work were associated with only slightly increased risk of early retirement [132], so it is not likely to bias the results.

That the study population of the present study is limited to only one profession could be a strength, as discussed in Section 5.2. However, in a study of working conditions in only one profession, the contrast in exposure could be lower than in a population of various professions. In the present study, only the category with strenuous OPA was rather small, but in many of the analyses the demanding and strenuous OPA categories were collapsed into a high OPA category comprising 46.3% of the study population. The exposure contrast thus seems to be sufficient, but might represent only a section of the exposure in the general population of workers.

Strengths of the present study also include the evaluation of both multiplicative and additive interaction. An advantage of additive models is that the output is an absolute measure of the number of cases that could potentially be prevented by eliminating the exposure in question [158].

Nurses with missing information about the main variables (OPA and psychosocial factors) were excluded from the study population, but there was missing information regarding some of the covariates. A sensitivity analysis showed that the age-adjusted association between OPA and IHD analysis among nurses with complete information about all covariates was comparable to the age-adjusted association between OPA and IHD among all 12,093 nurses. This result indicated that missing values were randomly distributed and did not affect the results.

Validity of measures of exposures

In a cohort study with a self-report measure, information bias (misclassification) and the validity of the measure of exposure are potential problems.

OPA question: The OPA measure used in the present study is based on the Saltin-Grimby OPA question [137], which is a single question that reflects the level of physical activity in four crude categories. The original intention of the question was to find associations between the overall level of OPA and health and physiological effects [138], which was also intended in the present study. The OPA question in the present study also includes the perception of the individual of the intensity of the workload (e.g., whether it is exerting, heavy or fast) and thus of the relative workload. It has been shown and discussed whether a relative OPA measure, rather than an absolute measure of OPA better captures the aspects of OPA that are associated with increased risk of atherosclerosis and heart disease [69;81;114]. This could be due to the capacity of a relative measure to capture the effect of a discrepancy between aerobic fitness and the physical demands of work [81].

The Saltin-Grimby OPA question has been shown to have acceptable validity when compared to a seven-day diary [85]. Furthermore, a recent study showed that the Saltin-Grimby OPA question explained 21% of the variance of the objectively-measured physical activity time, while a full prediction model, including age, gender, BMI, job group, OPA and occupational sedentary time explained 63% of the variation [170]. Taking these covariates into account could improve the performance of the OPA question and it could, therefore, theoretically perform better in a cohort of the same gender, education and occupation and with a limited age-span, as in the present study population.

The Saltin-Grimby OPA question is well known and seems to be useful in dividing the study population in broad categories of increasing level of physical activity and to show an association between increasing levels of OPA and increasing risk of IHD and all-cause mortality [32;33]. An objective measure might more accurately divide the participants into groups according to the level of locomotor activity, but an advantage of the self-report measure might be the ability to capture the discrepancy between physical capacity and the objective workload.

LTPA question: The Saltin and Grimby question about LTPA has been widely used in many epidemiological studies and surveys, especially in the Nordic countries [138]. The question has been shown to correspond well with LTPA measured by accelerometer and to have a moderate correlation with VO_{2max} [171]. Furthermore, a strong association between the question and a more detailed questionnaire of physical activity energy expenditure per week has been demonstrated [172]. In a recent review, it was concluded that the LTPA question is suitable for assessing physical activity at population level in four broad leisure time categories and is able to predict both cardiovascular risk factor profile including biomarkers, morbidity including CVD and mortality [138]. The question thus seems to be suitable for the purpose of present study, where division of the study population into broad categories of LTPA of increasing physical activity level was intended.

Hypertension: Hypertension status was self-reported and the actual blood pressure was thus not known. However, the percentage of nurses with hypertension in the present study was in accordance with the prevalence of hypertension in a comparable age group known from a Danish study [173].

Furthermore, the findings using this self-reported measure correspond to a comparable study with objectively measured blood pressure [38]. Furthermore, the reporting of medical conditions by nurses has been shown to be very accurate [174].

Influence at work: Influence at work was measured by a single question concerning the level of influence on the organisation of the daily work and, thus, only reflects this aspect of job control from Karasek's Demand-Control model. Job control has been shown to vary less within a single profession than psychological job demands [175]. This was also the case in the present study, where around 90% of the nurses had major or some influence at work, and this seems to be characteristic for the nursing profession. A better exposure contrast would have made it possible to examine the whole range of levels of influence at work instead of the dichotomous measure used.

Covariates: All covariates were self-reported, which will lead to some degree of misclassification. The size of the associations between the known risk factors for heart disease and IHD were, however, comparable to what is found in other epidemiological studies, e.g., the Copenhagen City Heart Study [176], and the adjustment for the covariates in the multivariable analyses can, therefore, be assumed to be acceptable.

Measurement at one point in time

It is not known whether the level of OPA exposure measured in 1993 remained the same during follow-up or was changed. A sensitivity analysis, however, indicated that exposure to OPA was rather stable over time regarding sedentary, moderate and demanding OPA and, to a lesser extent, regarding strenuous OPA. In accordance with this, two studies reported that measures of OPA were rather stable over time [69;114]. Changes in exposure during follow-up will lead to some extent of misclassification, but this will most likely be non-differential and lead to weaker associations [142;177]. A sensitivity analysis among nurses with the same level of OPA exposure in 1993 and 1999 indicated that there could be a dilution of the extent of the association between IHD and especially strenuous OPA due to change in exposure.

Confounding

Even in a relatively homogenous study population, such as the present study, civil status could be important in determining the household income and thereby the economic possibilities for many women. This might especially be the case for nurses, where around 30% of the nurses in 1993 had fewer than 30 hours of work per week, and thus a lower income. Adjustment for civil status, however, only slightly changed the estimates.

It strengthens the validity of the present study that LTPA and occupational factors, such as psychosocial work factors, working hours and shift work, as well as many relevant risk factors for IHD, were measured and could be adjusted for in the multivariable analyses. Nurses with strenuous OPA, however, seemed to differ from the other three OPA categories regarding the distribution of some of the covariates, such as BMI, work pressure, shift work and working hours per week. Adjustment for the covariates in the fully adjusted model attenuated the estimate of the association between high OPA and IHD somewhat, but it remained statistically significant. There might, however, still be residual confounding from unmeasured factors, which could explain some of the findings regarding strenuous OPA.

External validity

An important question is to what extent the results have relevance for other female professionals in Denmark and comparable countries. A study has been conducted that compares Danish nurses with the general female population, and the results indicated that, although nurses have a healthier lifestyle compared to other Danish women, the findings based on the cohort do seem to be generalizable to Danish women [45]. However, regarding occupational factors, there might be special aspects related to the work as a nurse, e.g., working with patients and relating to their problems, needs and expectations, and the hierarchical organisation at a hospital, as suggested by Siegrist in a comment from 2002 [178]. The physical activity pattern and other aspects of the physical demands in the nursing profession could be different from OPA in other professions. Danish nurses, though, have a range of different working conditions depending on the type of nursing work (e.g., hospital, nursing, homes, primary care, public health or teaching) and, therefore, the results could apply to other female health care workers. The results could also be of relevance for female health care workers in countries with working conditions comparable to Denmark.

5.7 Perspectives for further research

A number of recent studies among men, but only the present study and a few other studies among women have shown or indicated a detrimental association between high OPA and risk of IHD, CVD or all-cause mortality. Some of the studies that included both genders found different health effects of high OPA in men and women, and it is an open question whether there is a gender difference in the impact of high OPA on cardiovascular health or mortality. Future studies, specifically aimed at investigating this question, should be performed.

In the present study, OPA was assessed in four broad categories that was suitable for the purpose of the present study, but did not allow for more specific investigation of which aspects of OPA that were responsible for the detrimental effect of high OPA: was it is due to heavy static work, the pattern of OPA or the total amount and duration of exposure? Was it a mismatch between cardiorespiratory capacity and physical workload? And what roles do exhaustion and tiredness after work and lack of restitution play? Many unsolved questions remain and deserve further investigation. Objective methods for measuring physical activity have been developed, and this will make more detailed studies of the association between characteristics of OPA and health possible and, hopefully, lower the degree of misclassification of OPA. Though they are more expensive and less feasible than questionnaires, objective measures are now used in a number of large epidemiological studies. When the follow-up time is long enough to provide sufficient power in these studies, it will provide the opportunity to analyse the health effect of type, intensity and pattern of OPA on cardiovascular outcomes, both symptomatic outcomes, such as IHD, and asymptomatic outcomes, such as carotid artery intima-media thickness (IMT) or vascular stiffness.

An editorial from 2010 argued for using pre-existing cohorts with self-report measures to explore, e.g., the association between high OPA and CVD [21]. This might be a good way to provide and supplement the knowledge here and now, e.g., for use in meta-analyses. Furthermore, these studies could provide new information and generate new hypotheses about groups at particular risk, for example, different age groups or workers with pre-existing CVD, or about gender differences. They could furthermore be used for mediation analyses, to gain knowledge and create hypotheses about the pathways leading from high OPA to IHD and other types of CVD.

The finding that hypertensive nurses could have a particularly high risk of IHD from high OPA would be very interesting to investigate further, with respect to the impact of intensity of OPA and of static tasks, in future studies using objective measures of OPA and measured blood pressure. It would also be interesting to specifically investigate whether hypertensive workers with high OPA would also benefit from vigorous LTPA, or whether this could impose extra strain on the cardiovascular system.

The finding in the present study – that LTPA could affect the association between high OPA and IHD – needs to be further investigated, especially among women. Relatively little is known about whether there are solely beneficial effects for workers in physically demanding jobs of exercising to improve their cardiorespiratory fitness, or whether this could have unwanted effects, such as further strain on the cardiovascular system. This needs to be further investigated in future intervention studies.

Adverse psychosocial work factors, such as low job control, often coincide with high physical demands in the same occupations [179], but knowledge of their joint effect on the risk of cardiovascular disease is very sparse. The finding in the present study, and the finding of Clays el al. [40], of a potential detrimental interplay between high physical demands at work and low influence at work or low social support, respectively, and the risk of IHD, emphasize that this is a highly relevant area of research that needs to be further investigated.

5.8 Perspectives for the prevention of heart disease

Workers spend many hours at the workplace and are exposed to a number of risk factors for IHD, including high OPA. Prevention of IHD from high OPA can be directed at both the individual level (e.g., increasing physical activity during leisure time), the level of the workplace (decrease strenuous OPA or provide higher influence at work) and at the policy level, e.g., by recommendations and regulations targeted to workers with physically demanding work.

The results of a single observational study, although considered to have produced valid results, should be taken with precaution and cannot immediately be translated into preventive measures. It should be evaluated in the light of the existing knowledge, as there is always the possibility that findings arise by chance. The present study is one of only a few studies among women to find a detrimental effect of high OPA, and the absolute extent of the association between high OPA and IHD is modest. Furthermore, the crude nature of the OPA measure makes it difficult to pinpoint which aspects of high OPA are important for the detrimental effect and whether some of these are associated with an even higher risk of IHD. This inaccuracy makes it difficult to relate the results to prevention strategies.

The finding in the present study – that hypertensive women with high OPA might be at particular risk of IHD – is, however, a marked result that deserves attention, despite the fact that it is based on a single study. The general advice to individuals with hypertension is to engage in more than 30 minutes of physical activity with moderate intensity, at best, every day, primarily endurance training but supplemented with resistance training [180;181]. An advice based on the results of the present study is that workers with high OPA should be especially aware of their blood pressure and those with hypertension should be informed of the benefits of physical training with moderate intensity. The counteracting effect of LTPA on the association between high OPA and risk of IHD could also apply to individuals with hypertension, who would furthermore benefit from a known lowering effect on the blood pressure of LTPA. If the findings of the present study are confirmed in future studies, workers with hypertension in jobs with high OPA ought to be offered occupational health counselling about safe limits, e.g., for heavy static work tasks, and perhaps be offered ergonomic testing before engaging in physically strenuous work.

An important message to communicate from the results of the present study and the existing knowledge is that LTPA seems to be predominantly beneficial for all workers, including those with physically demanding work and, furthermore, that high OPA in many jobs is not of sufficient intensity to improve cardiorespiratory fitness, and does not have the same health-promoting effect as LTPA.

The findings of the present study – that high influence at work might counteract the increased risk of IHD from strenuous OPA – and the finding of Clays et al. of a buffering effect of social support at work indicate that prevention of IHD could be even more effective by directing prevention both towards lowering physical demands at work and towards improving psychosocial work factors, such as increased influence at work or improved social support at work.

Recommendations and regulations about high OPA must be made so that it is safe for the majority of workers, including any vulnerable groups, if such are identified, and must also include recommendations about the maximal duration and pauses between work tasks. For all workers, there might be a need for more personalised advice and health-promoting interventions that take gender, occupation and chronic disease, such as hypertension, into account [36].

6. CONCLUSION

This study among female Danish nurses suggests that high OPA is a risk factor for IHD among women. This finding is also suggested in a few former studies among women and in line with the findings in a number of recent studies among men. The finding in the present study of an increased risk of IHD from high OPA is supported by a low level of confounding from socio-economic factors, adjustment for many relevant potential confounders, and by the robustness of the finding in the sensitivity analyses, in which potential sources of bias were examined. The finding is also supported by a plausible physiological pathway from high OPA through atherosclerosis to IHD. It is not known, however, to what extent special working conditions among nurses could explain the findings, but high OPA as a risk factor for IHD could also apply to other female health care workers.

The results of the present study showed that the association between OPA and risk of IHD depended on the level of LTPA. Among nurses with high OPA, a trend towards a lower risk of IHD with an increasing level of LTPA – from sedentary through moderate to vigorous LTPA – was observed. This indicates that women with high OPA would benefit from a high level of LTPA, but it was also found that a high level of LTPA did not completely eliminate the increased risk associated with high OPA.

A modifying effect of hypertension on the relation between high OPA and risk of IHD was found. Hypertensive nurses with high OPA had a markedly increased risk of IHD, which was not observed among normotensive nurses. This indicates that hypertensive women might be at considerably higher risk of IHD from exposure to high OPA than normotensive women. This is one of very few studies that have investigated this question, and the first among women.

The examination of a possible modifying effect of influence at work on the association between high OPA and risk of IHD indicated that high influence at work could attenuate the risk of IHD among nurses with strenuous OPA. This suggests that improvement in psychosocial work factors – such as greater influence at work – among workers with physically strenuous work, could potentially add to the prevention of IHD and other cardiovascular diseases.

7. SUMMARY

Background

High occupational physical activity (OPA) has been linked to an increased risk of ischaemic heart disease (IHD) in men and in a few studies among women, but this association could be confounded by socioeconomic status. The majority of studies in women, however, suggest that OPA has either a protective effect or no association with risk of IHD. Consequently, it is not known whether high OPA is a risk factor for IHD among women.

Aim

The overall aim of the thesis was to investigate a possible association between high OPA and risk of IHD in female nurses aged 45 – 64. More specifically, objectives were to investigate whether high OPA is a risk factor for IHD (Study I a), and to test for effect modification by physical activity during leisure time (LTPA) (Study I b), hypertension (Study II) and high influence at work (Study III).

Design

A prospective, register-based cohort study.

Materials and methods

From the Danish Nurse Cohort Study, we identified 12,093 female nurses who, at baseline in 1993, were aged 45 – 64, were actively employed, had no prior hospital admission for IHD and had completed the questions about OPA and psychosocial work factors. Information on OPA, physical activity during leisure time, known risk factors for IHD and occupational factors at baseline in 1993 had been collected by way of a self-administered questionnaire. OPA was classified as sedentary, moderate, demanding or strenuous. Strenuous OPA and demanding OPA were collapsed into the category “high” in some of the analyses (Studies I and II). Information on incident hospitalisation with IHD during 15-year (Studies I and II) and 20-year (Study III) follow-up was obtained by individual linkage in the Danish National Patient Registry.

Cox proportional hazards models were used to investigate the association between exposure and risk of IHD and to test for multiplicative interaction. Additive interaction was also investigated in additive hazards models.

Results

A total of 580 nurses were hospitalized with IHD during the 15-year follow-up period and 869 during the 20-year follow-up period.

High physical activity at work was associated with increased risk of IHD. Compared to nurses with moderate OPA, those with demanding OPA had a 22% higher risk of IHD and nurses with strenuous OPA had a 41% higher risk of IHD.

The association between OPA and IHD differed according to the level of physical activity during leisure time. A graded increased risk of IHD was observed in the group of nurses with high OPA, depending on the level of physical activity during leisure time, which ranged from a 75% higher risk of IHD among those engaged in vigorous physical activity during leisure time to 2.6 times higher risk among those who were mainly sedentary during leisure time.

Hypertension modified the association between high OPA and IHD. Nurses with hypertension had almost a three times higher risk of IHD from high OPA, compared to normotensive nurses with moderate OPA. Normotensive nurses with high OPA did not have a significantly higher risk of IHD. In an additive hazards model, a significant additive interaction between hypertension and high OPA was found. This additive interaction explained 40 out of 60 additional cases of IHD per 10,000 person-years among hypertensive nurses with high OPA compared to normotensive nurses with moderate OPA.

A modifying effect of high influence at work on the association between strenuous OPA and risk of IHD was observed. Strenuous OPA in combination with low influence at work was associated with a higher risk of IHD, but this detrimental association was not found in combination with high influence at work. An additive hazards model investigating the association between different combinations of OPA and influence at work and IHD indicated a detrimental additive interaction between strenuous OPA and low influence at work.

Conclusion

This study suggests that high OPA is a risk factor for IHD among women. It further suggests that vigorous physical activity during leisure time could lower, but not completely eliminate, the increased risk of IHD among women with high OPA. The results also indicate that hypertensive women could be at particular risk of IHD from exposure to high OPA.

Furthermore, the present study suggests that high influence at work may buffer and thus counteract some of the adverse effects of strenuous OPA on risk of IHD.

8. DANSK RESUMÉ

Baggrund

Flere nyere undersøgelser blandt mænd og nogle få blandt kvinder har fundet at høj fysisk aktivitet på arbejdet (OPA) er forbundet med en forøget risiko for iskæmisk hjertesygdom (IHD). En mulig forklaring på denne sammenhæng kan være confounding fra socio-økonomiske faktorer. Flertallet af undersøgelser blandt kvinder har imidlertid ikke vist nogen sammenhæng mellem høj OPA og IHD, og enkelte har fundet at høj OPA har en beskyttende virkning. Det er derfor uklart, om høj OPA er en risikofaktor for IHD blandt kvinder. Endvidere ved vi ikke, om faktorer som fysisk aktivitet i fritiden eller høj grad af indflydelse på arbejdet, kan modvirke den skadelige virkning af høj OPA, eller om der er grupper som f.eks. kvinder med hypertension, der er i særlig risiko for IHD, når de har fysisk anstrengende arbejde.

Formål

Det overordnede formål med denne ph.d. afhandling var at undersøge sammenhængen mellem OPA og risiko for IHD blandt 45 til 64 årige kvindelige sygeplejersker. De specifikke mål var at undersøge, om høj OPA er en risikofaktor for IHD (studie I a) og at undersøge om sammenhængen mellem OPA og IHD modificeres af henholdsvis fysisk aktivitet i fritiden (studie I b), hypertension (studie II) og indflydelse på arbejdet (studie III).

Design

En prospektiv registerbaseret kohorteundersøgelse.

Materialer og metoder

Undersøgelsen var baseret på data fra Den Danske Sygeplejerskekohorte. Studiepopulationen bestod af 12 093 kvindelige sygeplejersker, som ved undersøgelsens start i 1993 var 45-64 år og var i aktiv beskæftigelse, som ikke tidligere havde været indlagt med IHD og som havde besvaret spørgsmålene om OPA og om psykosociale arbejdsfaktorer. Information om fysisk aktivitet på arbejdet og i fritiden, om kendte risikofaktorer for IHD og om arbejdsmiljøfaktorer blev indhentet via et spørgeskema, som sygeplejerskerne besvarede ved baseline i 1993. OPA blev klassificeret som stillesiddende, moderat, krævende eller anstrengende. De to sidstnævnte kategorier blev i nogle af analyserne slået sammen i kategorien høj OPA (studie I og II). Information om incidente tilfælde af IHD blev indhentet gennem 15 års opfølgning i studie I and II og and 20 års opfølgning i studie III ved individuel kobling til det danske Landspatientregister.

Sammenhængen mellem eksponering og risiko for IHD blev undersøgt i Cox proportional hazards modeller. Disse modeller blev også anvendt til at undersøge, om der var multiplikativ interaktion. Additive hazards modeller blev anvendt til at undersøge for additiv interaktion.

Resultater

I alt 580 af sygeplejerskerne i studiepopulationen blev hospitalsindlagt med første tilfælde af IHD i løbet af de 15 års opfølgning i studie I og II og 869 gennem de 20 års opfølgning i studie III.

Resultaterne viste, at høj OPA var forbundet med en højere risiko for IHD. Sygeplejersker med krævende OPA havde 22 % højere risiko for IHD og de med anstrengende OPA 41 % højere risiko for IHD sammenlignet med sygeplejersker, der havde moderat OPA.

Sammenhængen mellem OPA og IHD afhang af niveauet af fysisk aktivitet i fritiden. Blandt sygeplejersker med høj OPA var der en tendens til gradvis faldende risiko for IHD med stigende niveau af fysisk aktivitet i fritiden fra 2,6 gange højere risiko for IHD blandt de med stillesiddende aktiviteter i fritiden til 75 % gange højere blandt de, der var allermest aktive i fritiden. Et højt niveau af fysisk aktivitet i fritiden kunne således i nogen grad men ikke fuldstændig modvirke den forøgede risiko for IHD, der var ved at have høj OPA.

Sammenhængen mellem høj OPA og risiko for IHD var forskellig for sygeplejersker med hypertension og med normalt blodtryk. Sygeplejersker med hypertension og høj OPA havde næsten tre gange højere risiko for IHD end sygeplejesker med normalt blodtryk og moderat OPA. En sådan forhøjet risiko for IHD forbundet med høj OPA blev ikke fundet blandt sygeplejersker med normalt blodtryk. Blandt sygeplejersker med hypertension og høj OPA var der 60 ekstra tilfælde af IHD pr. 10 000 person år, sammenlignet med sygeplejersker med normalt blodtryk og moderat OPA. Over halvdelen af disse 60 tilfælde kunne forklares med additiv interaktion mellem hypertension og høj OPA, hvilket vil sige at kombinationen af hypertension og høj OPA førte til langt flere tilfælde af IHD end man ville forvente ud fra effekten af disse to faktorer hver for sig.

Analyserne af en eventuel modificerende effekt af indflydelse på arbejdet pegede overordnet på, at der var en skadelig sammenhæng mellem anstrengende OPA og IHD blandt sygeplejersker med lav indflydelse på arbejdet men ikke blandt de med høj indflydelse på arbejdet. Resultaterne indikerede, at dette kunne skyldes additiv interaktion mellem anstrengende OPA og lav indflydelse på arbejdet, der førte til flere tilfælde af IHD end forventet blandt sygeplejerskerne i denne gruppe.

Konklusion

Denne undersøgelse blandt kvindelige sygeplejersker viste, at høj OPA kan være en risikofaktor for IHD blandt kvinder. Ydermere viser undersøgelsen, at meget fysisk aktivitet i fritiden kan formindske, men ikke fuldstændig modvirke den forøgede risiko for IHD ved høj OPA.

Endvidere viste resultaterne, at kvinder med hypertension med høj OPA ser ud til at have en særlig stor risiko for IHD.

Endelig, kan høj indflydelse på arbejdet måske modvirke en skadelig sammenhæng mellem anstrengende OPA og risiko for IHD.

9. REFERENCE LIST

(1) O'Flatherty M, Sans-Menendez S, Capewell S, Jørgensen T. Epidemiology of atherosclerotic cardiovascular disease: scope of the problem and its determinants. In: Gielen S, Backer dG, Piepoli MF, Wood D, editors. The ESC textbook of Preventive Cardiology. Oxford: Oxford University press; 2015. 3-18.

(2) Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011; 124(19):2145-2154.

(3) Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006; 27(8):994-1005.

(4) Nicholas M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P et al. European Cardiovascular Disease Statistics 2012. 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis.

(5) Poulter N. Coronary heart disease is a multifactorial disease. *Am J Hypertens* 1999; 12(10 Pt 2):92S-95S.

(6) Belkic K, Schnall P, Landsbergis P, Baker D. The workplace and cardiovascular health: conclusions and thoughts for a future agenda. *Occup Med* 2000; 15(1):307-321.

(7) Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. *Scand J Work Environ Health* 2001; 27(3):161-213.

(8) Tuchsen F, Mikkelsen KL, Hannerz H, Poulsen OM, Bach E. Work environment and somatic hospital admissions in Denmark 1994-1999. *Sci Total Environ* 2004; 328(1-3):287-294.

(9) Eurofound. First findings:Sixth European Working Conditions Survey. Publications Office of the European Union, Luxembourg; 2015.

(10) Karlqvist L, Leijon O, Harenstam A. Physical demands in working life and individual physical capacity. *Eur J Appl Physiol* 2003; 89(6):536-547.

(11) Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953; 265(6795):1053-1057.

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

(13) Paffenbarger RS, Hale WE. Work activity and coronary heart mortality. *N Engl J Med* 1975; 292(11):545-550.

(14) Taylor HL, Klepetar E, Keys A, Parlin W, Blackburn H, Puchner T. Death rates among physically active and sedentary employees of the railroad industry. *Am J Public Health Nations Health* 1962; 52:1697-1707.

(15) Salonen JT, Puska P, Tuomilehto J. Physical activity and risk of myocardial infarction, cerebral stroke and death: a longitudinal study in Eastern Finland. *Am J Epidemiol* 1982; 115(4):526-537.

(16) Menotti A, Seccareccia F. Physical activity at work and job responsibility as risk factors for fatal coronary heart disease and other causes of death. *J Epidemiol Community Health* 1985; 39(4):325-329.

(17) Seccareccia F, Menotti A. Physical activity, physical fitness and mortality in a sample of middle aged men followed-up 25 years. *J Sports Med Phys Fitness* 1992; 32(2):206-213.

(18) Steenland K, Fine L, Belkic K, Landsbergis P, Schnall P, Baker D et al. Research findings linking workplace factors to CVD outcomes. *Occup Med* 2000; 15(1):7-68.

(19) Ilmarinen J. Work and cardiovascular health: viewpoint of occupational physiology. *Ann Med* 1989; 21(3):209-214.

(20) Li J, Loerbroks A, Angerer P. Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? *Curr Opin Cardiol* 2013; 28(5):575-583.

(21) Krause N. Physical activity and cardiovascular mortality--disentangling the roles of work, fitness, and leisure. *Scand J Work Environ Health* 2010; 36(5):349-355.

(22) Holtermann A. Occupational and leisure-time physical activity and coronary heart disease. *Occup Environ Med* 2015; 72(9):615-616.

(23) Li J, Siegrist J. Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health* 2012; 9(2):391-407.

(24) Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol* 2011; 40(5):1382-1400.

(25) Morris JN, Clayton DG, Everitt MG, Semmence AM, Burgess EH. Exercise in leisure time: coronary attack and death rates. *Br Heart J* 1990; 63(6):325-334.

(26) Kokkinos P. Physical activity, health benefits, and mortality risk. *ISRN Cardiol* 2012; 2012:718789.

(27) Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. *Sports Med* 2001; 31(2):101-114.

(28) Manson JE, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N Engl J Med* 1999; 341(9):650-658.

(29) Oguma Y, Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and all cause mortality in women: a review of the evidence. *Br J Sports Med* 2002; 36(3):162-172.

(30) Sattelmair J, Pertman J, Ding EL, Kohl HW, III, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; 124(7):789-795.

(31) Kukkonen-Harjula K. Physical activity and cardiovascular health-work and leisure differ. *Scand J Work Environ Health* 2007; 33(6):401-404.

(32) Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. The interplay between physical activity at work and during leisure time--risk of ischemic heart disease and all-cause mortality in middle-aged Caucasian men. *Scand J Work Environ Health* 2009; 35(6):466-474.

(33) Holtermann A, Marott JL, Gyntelberg F, Sogaard K, Suadicani P, Mortensen OS et al. Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. *BMJ Open* 2012; 2(1):e000556.

(34) Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Physical demands at work, physical fitness, and 30-year ischaemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 2010; 36(5):357-365.

(35) Clays E, De BD, Janssens H, De CB, Casini A, Braeckman L et al. The association between leisure time physical activity and coronary heart disease among men with different physical work demands: a prospective cohort study. *Eur J Epidemiol* 2013; 28:241-247.

(36) Williamson W, Boardman H, Lewandowski AJ, Leeson P. Time to rethink physical activity advice and blood pressure: A role for occupation-based interventions? *Eur J Prev Cardiol* 2016; 23(10):1051-1053.

(37) Virkkunen H, Harma M, Kauppinen T, Tenkanen L. Shift work, occupational noise and physical workload with ensuing development of blood pressure and their joint effect on the risk of coronary heart disease. *Scand J Work Environ Health* 2007; 33(6):425-434.

(38) Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Physical work demands, hypertension status, and risk of ischemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 2010; 36(6):466-472.

(39) Clays E, De BD, Van HK, De BG, Kittel F, Holtermann A. Occupational and leisure time physical activity in contrasting relation to ambulatory blood pressure. *BMC Public Health* 2012; 12:1002.

(40) Clays E, Casini A, Van Herck K, De Bacquer D, Kittel F, De Backer G et al. Do psychosocial job resources buffer the relation between physical work demands and coronary heart disease? A prospective study among men. *Int Arch Occup Environ Health* 2016; doi: 10.1007/s00420-016-1165-z.

(41) Beenackers MA, Kamphuis CB, Giskes K, Brug J, Kunst AE, Burdorf A et al. Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: a systematic review. *Int J Behav Nutr Phys Act* 2012; 9:116.

(42) Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation* 1993; 88(4 Pt 1):1973-1998.

(43) Marmot MG, Kogevinas M, Elston MA. Social/economic status and disease. *Annu Rev Public Health* 1987; 8:111-135.

(44) Virtanen SV, Notkola V. Socioeconomic inequalities in cardiovascular mortality and the role of work: a register study of Finnish men. *Int J Epidemiol* 2002; 31(3):614-621.

(45) Hundrup YA, Simonsen MK, Jorgensen T, Obel EB. Cohort profile: the Danish nurse cohort. *Int J Epidemiol* 2012; 41(5):1241-1247.

(46) Khaw KT. Epidemiology of coronary heart disease in women. In: Julian DG, Wenger NK, editors. Women & Heart Disease. first ed. London: Martin Dunitz; 1997. 7-20.

(47) Maas AH, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J* 2010; 18(12):598-602.

(48) Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. *Eur Heart J* 2000; 21(14):1141-1151.

(49) Muennig P, Sohler N, Mahato B. Socioeconomic status as an independent predictor of physiological biomarkers of cardiovascular disease: evidence from NHANES. *Prev Med* 2007; 45(1):35-40.

(50) Kaplan GA, Sallis JF, Patterson TL. Cardiovascular diseases. In: Kaplan GA, Patterson TL, editors. Health and human behaviour. Singapore: McGraw-Hill; 1993. 206-242.

(51) Keaney JF, Jr. Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction. *Mol Aspects Med* 2000; 21(4-5):99-166.

(52) Landmesser U, Koenig W. From risk factors to plaque development and plaque destabilization. In: Gielen S, Backer dG, Piepoli MF, Wood D, editors. The ESC Textbook of Preventive Cardiology. Oxford: Oxford University Press; 2015. 26-29.

(53) Faioni EM, Lettino M, Cattaneo M. The role of thrombosis. In: Gielen S, Backer dG, Piepoli MF, Wood D, editors. The ESC Textbook of Preventive Cardiology. Oxford: Oxford University Press; 2015. 30-35.

(54) Bittner V. Women and coronary heart disease risk factors. *J Cardiovasc Risk* 2002; 9(6):315-322.

(55) Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364(9438):937-952.

(56) Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. *Med Sci Sports Exerc* 2012; 44(1 Suppl 1):S5-12.

(57) Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc* 2001; 33(6 Suppl):S364-S369.

(58) Haskell WL. What to look for in assessing responsiveness to exercise in a health context. *Med Sci Sports Exerc* 2001; 33(6 Suppl):S454-S458.

(59) Sogaard K, Sjogaard G. Physiological Bases of Work Assessment. In: Wilson JR, Sharples S, editors. Evaluation of Human Work. 4 ed. London: C R C Press LLC; 2015. 419-445.

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

(61) Blair SN, Kampert JB, Kohl HW, III, Barlow CE, Macera CA, Paffenbarger RS, Jr. et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996; 276(3):205-210.

(62) Ilmarinen J, Louhevaara V, Korhonen O, Nygard CH, Hakola T, Suvanto S. Changes in maximal cardiorespiratory capacity among aging municipal employees. *Scand J Work Environ Health* 1991; 17 Suppl 1:99-109.

(63) Korshoj M, Krustrup P, Jespersen T, Sogaard K, Skotte JH, Holtermann A. A 24-h assessment of physical activity and cardio-respiratory fitness among female hospital cleaners: a pilot study. *Ergonomics* 2013; 56(6):935-943.

(64) Krause N, Lynch JW, Kaplan GA, Cohen RD, Salonen R, Salonen JT. Standing at work and progression of carotid atherosclerosis. *Scand J Work Environ Health* 2000; 26(3):227-236.

(65) Dasinger LK, Krause N, Brand RJ, Kaplan GA, Salonen JT. Percent time at work in an upright posture associated with 11-year change in systolic blood pressure. 4th International Conference on Work Environment and Cardiovascular Diseases; March 9-11; 2005.

(66) Ilmarinen J. Physical load on the cardiovascular system in different work tasks. *Scand J Work Environ Health* 1984; 10(6 Spec No):403-408.

(67) Jorgensen K. Permissible loads based on energy expenditure measurements. *Ergonomics* 1985; 28(1):365-369.

(68) Bonjer FH. Encyclopedia of Occupational Health and Safety. second ed. Geneva: International Labour Organisation; 1971.

(69) Krause N, Brand RJ, Kaplan GA, Kauhanen J, Malla S, Tuomainen TP et al. Occupational physical activity, energy expenditure and 11-year progression of carotid atherosclerosis. *Scand J Work Environ Health* 2007; 33(6):405-424.

(70) Aittomaki A, Lahelma E, Roos E, Leino-Arjas P, Martikainen P. Gender differences in the association of age with physical workload and functioning. *Occup Environ Med* 2005; 62(2):95-100.

(71) Andersen Y. Sundhedsprofil af danske sygeplejersker. København: Dansk Institut for Sundheds- og Sygeplejerskeforskning; 1995.

(72) Wethje A, Borg W. Sygeplejerskers arbejdsmiljø, trivsel of helbred (SATH). 2006. København, Dansk Sygeplejeråd og Arbejdsmiljøinstituttet.

(73) Petersen CB, Eriksen L, Tolstrup JS, Sogaard K, Gronbaek M, Holtermann A. Occupational heavy lifting and risk of ischemic heart disease and all-cause mortality. *BMC Public Health* 2012; 12:1070.

(74) Hu GC, Chien KL, Hsieh SF, Chen CY, Tsai WH, Su TC. Occupational versus leisure-time physical activity in reducing cardiovascular risks and mortality among ethnic Chinese adults in Taiwan. *Asia Pac J Public Health* 2014; 26(6):604-613.

(75) Hu G, Jousilahti P, Borodulin K, Barengo NC, Lakka TA, Nissinen A et al. Occupational, commuting and leisure-time physical activity in relation to coronary heart disease among middle-aged Finnish men and women. *Atherosclerosis* 2007; 194(2):490-497.

(76) Barengo NC, Hu G, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 2004; 25(24):2204-2211.

(77) Lapidus L, Bengtsson C. Socioeconomic factors and physical activity in relation to cardiovascular disease and death. A 12 year follow up of participants in a population study of women in Gothenburg, Sweden. *Br Heart J* 1986; 55(3):295-301.

(78) Graff-Iversen S, Selmer R, Sorensen M, Skurtveit S. Occupational physical activity, overweight, and mortality: a follow-up study of 47,405 Norwegian women and men. *Res Q Exerc Sport* 2007; 78(3):151-161.

(79) Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS. Physical activity and incidence of coronary heart disease in middle-aged women and men. *Med Sci Sports Exerc* 1997; 29(7):901-909.

(80) Harari G, Green MS, Zelber-Sagi S. Combined association of occupational and leisure-time physical activity with all-cause and coronary heart disease mortality among a cohort of men followed-up for 22 years. *Occup Environ Med* 2015; 72(9):617-624.

(81) Krause N, Brand RJ, Arah OA, Kauhanen J. Occupational physical activity and 20-year incidence of acute myocardial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. *Scand J Work Environ Health* 2015; 41(2):124-139.

(82) Kristal-Boneh E, Harari G, Melamed S, Froom P. Association of physical activity at work with mortality in Israeli industrial employees: the CORDIS study. *J Occup Environ Med* 2000; 42(2):127-135.

(83) Salonen JT, Slater JS, Tuomilehto J, Rauramaa R. Leisure time and occupational physical activity: risk of death from ischemic heart disease. *Am J Epidemiol* 1988; 127(1):87-94.

(84) Virkkunen H, Harma M, Kauppinen T, Tenkanen L. The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease. *Occup Environ Med* 2006; 63(6):378-386.

(85) Stender M, Hense HW, Doring A, Keil U. Physical activity at work and cardiovascular disease risk: results from the MONICA Augsburg study. *Int J Epidemiol* 1993; 22(4):644-650.

(86) Rosengren A, Wilhelmsen L. Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Goteborg. *Ann Epidemiol* 1997; 7(1):69-75.

(87) Eaton CB, Medalie JH, Flocke SA, Zyzanski SJ, Yaari S, Goldbourt U. Self-reported physical activity predicts long-term coronary heart disease and all-cause mortalities. Twenty-one-year follow-up of the Israeli Ischemic Heart Disease Study. *Arch Fam Med* 1995; 4(4):323-329.

(88) Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. *Am Heart J* 1985; 110(5):1100-1107.

(89) Yu S, Yarnell JW, Sweetnam PM, Murray L. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart* 2003; 89(5):502-506.

(90) Johansson S, Rosengren A, Tsipogianni A, Ulvenstam G, Wiklund I, Wilhelmsen L. Physical inactivity as a risk factor for primary and secondary coronary events in Goteborg, Sweden. *Eur Heart J* 1988; 9 Suppl L:8-19.

(91) Sobolski J, Kornitzer M, De BG, Dramaix M, Abramowicz M, Degre S et al. Protection against ischemic heart disease in the Belgian Physical Fitness Study: physical fitness rather than physical activity? *Am J Epidemiol* 1987; 125(4):601-610.

(92) Holtermann A, Burr H, Hansen JV, Krause N, Sogaard K, Mortensen OS. Occupational physical activity and mortality among Danish workers. *Int Arch Occup Environ Health* 2012; 85(3):305-310.

(93) Richard A, Martin B, Wanner M, Eichholzer M, Rohrmann S. Effects of leisure-time and occupational physical activity on total mortality risk in NHANES III according to sex, ethnicity, central obesity, and age. *J Phys Act Health* 2015; 12(2):184-192.

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

(95) Lissner L, Bengtsson C, Bjorkelund C, Wedel H. Physical activity levels and changes in relation to longevity. A prospective study of Swedish women. *Am J Epidemiol* 1996; 143(1):54-62.

(96) Clays E, Lidegaard M, De Bacquer D, Van Herck K, De Backer G, Kittel F et al. The Combined Relationship of Occupational and Leisure-Time Physical Activity With All-Cause Mortality Among Men, Accounting for Physical Fitness. *Am J Epidemiol* 2013; 179(5):559-566.

(97) Boushel R. Muscle metaboreflex control of the circulation during exercise. *Acta Physiol (Oxf)* 2010; 199(4):367-383.

(98) Åstrand P, Rodahl K, Dahl H, Strømme S. Textbook of Work Physiology. Fourth ed. Human Kinetics; 2003.

(99) Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* 1988; 112(10):1018-1031.

(100) Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev* 1995; 75(3):519-560.

(101) Alexander RW. Theodore Cooper Memorial Lecture. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. *Hypertension* 1995; 25(2):155-161.

(102) Föex P, Sear JW. Hypertension: patophysiology and treatment. *Continuing Education in Anaesthesia, Critical Care & Pain* 2004; 4(3):71-75.

(103) Franz IW. Blood pressure response to exercise in normotensives and hypertensives. *Can J Sport Sci* 1991; 16(4):296-301.

(104) MacDougall JD, Tuxen D, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. *J Appl Physiol (1985)* 1985; 58(3):785-790.

(105) Willich SN, Lewis M, Lowel H, Arntz HR, Schubert F, Schroder R. Physical exertion as a trigger of acute myocardial infarction. Triggers and Mechanisms of Myocardial Infarction Study Group. *N Engl J Med* 1993; 329(23):1684-1690.

(106) Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 1993; 329(23):1677-1683.

(107) Hallqvist J, Moller J, Ahlbom A, Diderichsen F, Reuterwall C, De FU. Does heavy physical exertion trigger myocardial infarction? A case-crossover analysis nested in a population-based case-referent study. *Am J Epidemiol* 2000; 151(5):459-467.

(108) Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006; 174(6):801-809.

(109) Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008; 15(3):239-246.

(110) Wilson MG, Ellison GM, Cable NT. Basic science behind the cardiovascular benefits of exercise. *Br J Sports Med* 2016; 50(2):93-99.

(111) U.S.Department of Health and Human Services. Physical Activity and Health. 1996. Atlanta, U.S.Department of Health and Human Services.

(112) Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* 2005; 46(4):667-675.

(113) Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2002; 136(7):493-503.

(114) Wang A, Arah OA, Kauhanen J, Krause N. Effects of leisure-time and occupational physical activities on 20-year incidence of acute myocardial infarction: mediation and interaction. *Scand J Work Environ Health* 2016; 42(5):423-434.

(115) Poulter NR, Prabhakaran D, Caulfield M. Hypertension. *Lancet* 2015; 386(9995):801-812.

(116) Fagard R, Mancia G, Cifkova R. Blood Pressure. In: Gielen S, Backer dG, Piepoli MF, Wood D, editors. The ESC Textbook of Preventive Cardiology. Oxford: Oxford University Press; 2015. 189-200.

(117) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360(9349):1903-1913.

(118) Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003; 289(18):2363-2369.

(119) Karasek R, Theorell T. Healthy work. Stress, productivity and the reconstruction of working life. 1990. New York, Basic Books.

(120) Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. *J Occup Health Psychol* 1998; 3(4):322-355.

(121) Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB, Sr., Benjamin EJ. Does job strain increase the risk for coronary heart disease or death in men and women? The Framingham Offspring Study. *Am J Epidemiol* 2004; 159(10):950-958.

(122) Andersen I, Burr H, Kristensen TS, Gamborg M, Osler M, Prescott E et al. Do factors in the psychosocial work environment mediate the effect of socioeconomic position on the risk of

myocardial infarction? Study from the Copenhagen Centre for Prospective Population Studies. *Occup Environ Med* 2004; 61(11):886-892.

(123) Hammar N, Alfredsson L, Johnson JV. Job strain, social support at work, and incidence of myocardial infarction. *Occup Environ Med* 1998; 55(8):548-553.

(124) Lee S, Colditz G, Berkman L, Kawachi I. A prospective study of job strain and coronary heart disease in US women. *Int J Epidemiol* 2002; 31(6):1147-1153.

(125) Kuper H, Marmot M. Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. *J Epidemiol Community Health* 2003; 57(2):147-153.

(126) Levi L, Bartley M, Marmot M, Karasek R, Theorell T, Siegrist J et al. Stressors at the workplace: theoretical models. *Occup Med* 2000; 15(1):69-106.

(127) Kasl SV. The influence of the work environment on cardiovascular health: a historical, conceptual, and methodological perspective. *J Occup Health Psychol* 1996; 1(1):42-56.

(128) Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A. Is the effect of job strain on myocardial infarction risk due to interaction between high psychological demands and low decision latitude? Results from Stockholm Heart Epidemiology Program (SHEEP). *Soc Sci Med* 1998; 46(11):1405-1415.

(129) Devereux JJ, Vlachonikolis IG, Buckle PW. Epidemiological study to investigate potential interaction between physical and psychosocial factors at work that may increase the risk of symptoms of musculoskeletal disorder of the neck and upper limb. *Occup Environ Med* 2002; 59(4):269-277.

(130) Devereux JJ, Buckle PW, Vlachonikolis IG. Interactions between physical and psychosocial risk factors at work increase the risk of back disorders: an epidemiological approach. *Occup Environ Med* 1999; 56(5):343-353.

(131) Alfredsson L, Spetz CL, Theorell T. Type of occupation and near-future hospitalization for myocardial infarction and some other diagnoses. *Int J Epidemiol* 1985; 14(3):378-388.

(132) Friis K, Ekholm O, Hundrup YA, Obel EB, Gronbaek M. Influence of health, lifestyle, working conditions, and sociodemography on early retirement among nurses: the Danish Nurse Cohort Study. *Scand J Public Health* 2007; 35(1):23-30.

(133) Dansk Sygeplejeråd. Fakta om sygeplejerskerne. *Tillæg til Tidsskrift for Sygeplejersker* 2001; 47:1-25.

(134) Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; 7:449-490.

(135) Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* 2003; 56(2):124-130.

(136) Videbæk J, Andersen LV, Bentzen J. Hjertestatistik. København: Hjerteforeningen; 2010.

(137) Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. *Circulation* 1968; 38(6):1104-1115.

(138) Grimby G, Borjesson M, Jonsdottir IH, Schnohr P, Thelle DS, Saltin B. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports* 2015; 25 Suppl 4:119-125.

(139) Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009; 41(5):998-1005.

(140) Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE et al. Daily sitting time and all-cause mortality: a meta-analysis. *PLoS One* 2013; 8(11):e80000.

(141) Stamatakis E, Chau JY, Pedisic Z, Bauman A, Macniven R, Coombs N et al. Are sitting occupations associated with increased all-cause, cancer, and cardiovascular disease mortality risk? A pooled analysis of seven British population cohorts. *PLoS One* 2013; 8(9):e73753.

(142) Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins; 1998.

(143) Allesoe K, Hundrup YA, Thomsen JF, Osler M. Psychosocial work environment and risk of ischaemic heart disease in women: the Danish Nurse Cohort Study. *Occup Environ Med* 2010; 67(5):318-322.

(144) Schnall PL, Landsbergis PA, Baker D. Job strain and cardiovascular disease. *Annu Rev Public Health* 1994; 15:381-411.

(145) Krause N, Brand RJ, Kauhanen J, Kaplan GA, Syme SL, Wong CC et al. Work time and 11-year progression of carotid atherosclerosis in middle-aged Finnish men. *Prev Chronic Dis* 2009; 6(1). http://www.cdc.gov/pdc/issues/2009/jan/07_0270.htm.

(146) Sokejima S, Kagamimori S. Working hours as a risk factor for acute myocardial infarction in Japan: case-control study. *BMJ* 1998; 317(7161):775-780.

(147) Kivimaki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L et al. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. *Lancet* 2015; 386(10005):1739-1746.

(148) Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE et al. Shift work and vascular events: systematic review and meta-analysis. *BMJ* 2012; 345:e4800.

(149) Kleinbaum DG, Klein M. Survival Analysis. Third ed. New York: Springer; 2012.

(150) Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; 145(1):72-80.

(151) Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer* 2004; 91(7):1229-1235.

(152) Rothman KJ. Epidemiology - an introduction. first ed. Oxford: Oxford University Press; 2002.

(153) VanderWeele TJ, Knol MJ. A Tutorial on Interaction. *Epidemiologic Methods* 2014; 3(1):33-72.

(154) von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007; 18(6):800-804.

(155) Vandenbroucke JP, von EE, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; 18(6):805-835.

(156) Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* 2012; 41(2):514-520.

(157) Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol* 2005; 20(7):575-579.

(158) Rod NH, Lange T, Andersen I, Marott JL, Diderichsen F. Additive interaction in survival analysis: use of the additive hazards model. *Epidemiology* 2012; 23(5):733-737.

(159) Li R, Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol* 2007; 17(3):227-236.

(160) Fransson E, De FU, Ahlbom A, Reuterwall C, Hallqvist J, Alfredsson L. The risk of acute myocardial infarction: interactions of types of physical activity. *Epidemiology* 2004; 15(5):573-582.

(161) Pedersen LR, Frestad D, Michelsen MM, Mygind ND, Rasmusen H, Suhrs HE et al. Risk Factors for Myocardial Infarction in Women and Men: A Review of the Current Literature. *Curr Pharm Des* 2016; 22(25):3835-3852.

(162) Ilmarinen J, Rutenfranz J. Occupationally induced stress, strain and peak loads as related to age. *Scand J Work Environ Health* 1980; 6(4):274-282.

(163) Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. *Aviat Space Environ Med* 1990; 61(1):3-11.

(164) Johnsen AM, Alfredsson L, Knutsson A, Westerholm PJ, Fransson EI. Association between occupational physical activity and myocardial infarction: a prospective cohort study. *BMJ Open* 2016; 6(10):e012692.

(165) van Uffelen JG, Wong J, Chau JY, van der Ploeg HP, Riphagen I, Gilson ND et al. Occupational sitting and health risks: a systematic review. *Am J Prev Med* 2010; 39(4):379-388.

(166) van der Ploeg HP, Moller SV, Hannerz H, van der Beek AJ, Holtermann A. Temporal changes in occupational sitting time in the Danish workforce and associations with all-cause mortality: results from the Danish work environment cohort study. *Int J Behav Nutr Phys Act* 2015; 12:71.

(167) Holtermann A, Hansen JV, Burr H, Sogaard K, Sjogaard G. The health paradox of occupational and leisure-time physical activity. *Br J Sports Med* 2012; 46(4):291-295.

(168) Holtermann A, Marott JL, Gyntelberg F, Sogaard K, Suadicani P, Mortensen OS et al. Does the benefit on survival from leisure time physical activity depend on physical activity at work? A prospective cohort study. *PLoS One* 2013; 8(1):e54548.

(169) Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* 2009; 20(4):488-495.

(170) Gupta N, Heiden M, Mathiassen SE, Holtermann A. Prediction of objectively measured physical activity and sedentariness among blue-collar workers using survey questionnaires. *Scand J Work Environ Health* 2016; 42(3):237-245.

(171) Emaus A, Degerstrom J, Wilsgaard T, Hansen BH, Dieli-Conwright CM, Furberg AS et al. Does a variation in self-reported physical activity reflect variation in objectively measured physical activity, resting heart rate, and physical fitness? Results from the Tromso study. *Scand J Public Health* 2010; 38(5 Suppl):105-118.

(172) Jorgensen L, Morseth B, Andreassen M, Jacobsen BK. Comments to Emaus et al. "Does a variation in self-reported physical activity reflect variation in objectively measured physical activity, resting heart rate, and physical fitness? Results from the Tromso study". *Scand J Public Health* 2011; 39(4):437-438.

(173) Kronborg CN, Hallas J, Jacobsen IA. Prevalence, awareness, and control of arterial hypertension in Denmark. *J Am Soc Hypertens* 2009; 3(1):19-24.

(174) Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health* 1997; 6(1):49-62.

(175) Kasl SV. Measuring job stressors and studying the health impact of the work environment: an epidemiologic commentary. *J Occup Health Psychol* 1998; 3(4):390-401.

(176) Holtermann A, Mortensen OS, Sogaard K, Gyntelberg F, Suadicani P. Risk factors for ischaemic heart disease mortality among men with different occupational physical demands. A 30-year prospective cohort study. *BMJ Open* 2012; 2(1):e000279.

(177) Hennekens CH, Buring JE. Epidemiology in Medicine. first ed. Philadelphia: Lippincott, Williams & Wilkins; 1987.

(178) Siegrist J. Commentatory: work stress and coronary heart disease - a gender (role) specific association. *Am J Epidemiol* 2002; 31(6):1154.

(179) Karlqvist LK, Harenstam A, Leijon O, Scheele P. Excessive physical demands in modern worklife and characteristics of work and living conditions of persons at risk. *Scand J Work Environ Health* 2003; 29(5):363-377.

(180) Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc* 2004; 36(3):533-553.

(181) Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. *Eur J Cardiovasc Prev Rehabil* 2007; 14(1):12-17.

10. APPENDICES

10.1. List of Abbreviations

BMI: Body mass index

CI: Confidence Interval

Cox PH model: Cox proportional hazards model

CVD: Cardiovascular disease

DNO: Danish Nurses Association

HR: Hazard ratio

ICD: International Classification of Diseases

IHD: Ischaemic heart disease

LTPA: Leisure time physical activity

MI: Myocardial infarction

OPA: Occupational physical activity

RERI: Relative excess risk due to additive interaction

U: Units

Wk: Week

10.2 Questionnaire from the 1993 Danish Nurse Cohort Study

2. Hvad er din ægteskabelige stilling rent juridisk?

Gift	1	☐	Gå til spm 4
Separeret	2	☐	
Skilt	3	☐	
Ugift	4	☐	
Enke	5	☐	

3. Bor du fast sammen i papirløst samliv?

Ja ☐

Nej ☐

6. Hvad er din erhvervsmæssige stilling?

Kun ét svar

Erhvervsaktiv som sygeplejerske	1	☐	Gå til spm 7
Erhvervsaktiv, men ikke som sygeplejerske	2	☐	Gå til spm 7
Efterlønsmodtager	3	☐	Gå til spm 14
Førtidspensionist	4	☐	Gå til spm 14
Folkepensionist	5	☐	Gå til spm 14
Hjemmegående	6	☐	Gå til spm 14
Arbejdsløs	7	☐	Gå til spm 14
Under revalidering	8	☐	Gå til spm 14

8. **Hvor mange timers erhvervsarbejde har du normalt om ugen?**
(Hvis den ugentlige arbejdstid varierer, angiv da gennemsnittet)

Angiv i hele timer . . . . ☐☐

9. **Arbejder du normalt i:** (Kun ét svar)

Dagvagt?	1	☐	Nattevagt?	3	☐
Aftenvagt?	2	☐	Blandede vagter?	4	☐

10. Nedenfor er fire udsagn. Hvilket passer bedst på din arbejdssituation?

Kun ét svar

Hovedsageligt stillesiddende arbejde, som ikke kræver legemlig anstrengelse	1	☐
Arbejde, som i stor udstrækning udføres stående eller gående, men ellers ikke kræver legemlig anstrengelse	2	☐
Stående eller gående arbejde med en del løfte- eller bærearbejde	3	☐
Tungt eller hurtigt arbejde, som er anstrengende	4	☐

12. Hvordan er arbejdstempoet eller arbejdspresset på dit arbejde?

(Kun ét svar)

Alt for højt	Lidt for højt	Passende	Lidt for lavt	Alt for lavt
☐	☐	☐	☐	☐

13. Hvor stor indflydelse har du normalt på tilrettelæggelsen af dit daglige arbejde?

(Kun ét svar)

Stor indflydelse	En vis indflydelse	Meget lidt indflydelse	Ingen indflydelse
☐	☐	☐	☐

14. Hvor meget vejer du?
(Angiv hele kilo)

☐☐☐ kilo

15. Hvor høj er du?
(Angiv hele cm.)

☐☐☐ cm.

16. Hvorledes vil du vurdere din nuværende helbredstilstand i almindelighed?
(Kun ét svar)

Meget god	God	Nogen-lunde	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

22. Hvilket af følgende udsagn passer bedst på dig?
(Læs alle udsagnene igennem, før du sætter ét kryds)

	Kun ét svar	
Træner hårdt og driver konkurrenceidræt regelmæssigt og flere gange om ugen	1	☐
Dyrker motionsidræt, udfører tungt havearbejde, husarbejde eller lignende mindst 4 timer pr. uge	2	☐
Spadserer, cykler eller har anden lettere motion mindst 4 timer pr. uge (medregn også søndagsture, lettere havearbejde og cykling/gang til arbejde)	3	☐
Læser, ser på fjernsyn eller har anden stillesiddende beskæftigelse	4	☐

25. Ryger du?

Kun ét svar

Ja, dagligt	1 ☐	
Ja, men der er dage, hvor jeg ikke ryger	2 ☐	
Nej, men jeg har røget tidligere	3 ☐	
Nej, har aldrig røget	4 ☐	Gå til spm 29
Ved ikke	5 ☐	

32. Hvor meget øl, vin eller spiritus drak du på hele dagen den seneste hverdag? (mandag - torsdag)

(Svar på **hvert** af underspørgsmålene. Hvis der ikke er drukket noget, skriv 0)

	Antal hele flasker		Antal hele glas
Almindelig øl	☐☐	Rød- el. hvidvin	☐☐
Stærk øl	☐☐	Hedvin	☐☐
		Spiritus	☐☐

33. Hvor meget øl, vin eller spiritus drak du i alt i den sidste weekend? (dvs. fredag, lørdag, søndag tilsammen)

(Svar på **hvert** af underspørgsmålene. Hvis der ikke er drukket noget, skriv 0)

	Antal hele flasker		Antal hele glas
Almindelig øl	☐☐	Rød- el. hvidvin	☐☐
Stærk øl	☐☐	Hedvin	☐☐
		Spiritus	☐☐

38. Har du inden for de sidste 14 dage taget nogle af de følgende former for medicin?

	Ja	Nej		Ja	Nej
a. Hostemedicin/ næsedråber	☐	☐	b. Blodtrykssænkende medicin	☐	☐
c. Hjertemedicin (nitro-glycerin, digoxin m.m.)	☐	☐	d. Salve eller andet hudlægemiddel	☐	☐
e. Smertestillende med.	☐	☐	f. Sovemidler	☐	☐
g. Afføringsmidler	☐	☐	h. Nervemidler, beroligende medicin	☐	☐
i. Kolesterolsænkende medicin	☐	☐	j. Kalktabletter	☐	☐
k. Naturmedicin	☐	☐	l. Vanddrivende medicin	☐	☐
m. Mavesårsmedicin	☐	☐	n. Andet	☐	☐

Skriv hvad: ____________________

41. Hvor mange *kvinder* i din familie er død af blodprop i hjertet, før de fyldte 65 år? Hvis ingen skriv 0

Antal (søstre, kusiner, fastre, mostre, mor, mormor) . . . . 1 ☐☐

Ved ikke . . . . 8 ☐

42. Har du, eller har du haft nedennævnte sygdomme?

	Ja	Nej		Ja	Nej
a. Blodprop i hjertet	☐	☐	b. Åreforkalkning i arterierne i benene	☐	☐
c. Åreknuder	☐	☐	d. Forhøjet blodtryk	☐	☐
e. Årebetændelse	☐	☐	f. Epilepsi	☐	☐
g. Hjerneblødning	☐	☐	h. Migræne	☐	☐
i. Andre neurologiske sygdomme	☐	☐	j. Recidiverende blærebetændelse	☐	☐
k. Stofskiftesygdom	☐	☐	l. Sukkersyge	☐	☐
m. Psykiatrisk lidelse	☐	☐	n. Gigt i hofter el. knæ	☐	☐

10.3 Questionnaire from the 1999 Danish Nurse Cohort Study

2. Hvad er din nuværende ægteskabelige stilling rent juridisk?

(Sæt kun ét kryds)

Gift .... ☐ 1

Separeret .... ☐ 2

Skilt .... ☐ 3

Ugift .... ☐ 4

Enke .... ☐ 5

3. Bor du sammen med ægtefælle/fast samlever?

Ja .... ☐ 1

Nej .... ☐ 2 Gå til spm. 5A

6. Hvor stor var din husstands samlede bruttoindkomst i 1998 (før skat og fradrag)?

(Ved din husstand forstår vi dig selv, din evt. ægtefælle/samlever og hjemmeboende børn)

(Sæt kun ét kryds)

Under 100.000 kr.	☐	01
100.000-199.000 kr.	☐	02
200.000-299.000 kr.	☐	03
300.000-399.000 kr.	☐	04
400.000-499.000 kr.	☐	05
500.000-599.000 kr.	☐	06
600.000-699.000 kr.	☐	07
Over 700.000 kr.	☐	08
Ved ikke	☐	88

ARTICLE 1.

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High occupational physical activity and risk of ischaemic heart disease in women: The interplay with physical activity during leisure time

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Abstract

Background: Recent studies indicate that physically demanding work is a risk factor for heart disease among men, especially those with low or moderate physical activity during leisure time. Among women, present evidence is inconclusive.

Design: The design was a prospective cohort study.

Methods: This investigation in the Danish Nurse Cohort Study included 12,093 female nurses aged 45–64 years, who answered a self-report questionnaire on physical activity at work and during leisure time, known risk factors for ischaemic heart disease (IHD) and occupational factors at baseline in 1993. Information on the 15-year incidence of IHD was obtained by individual linkage in the National Register of Hospital Discharges to 2008.

Results: During follow-up 580 participants were hospitalised with IHD. A significant interaction between occupational and leisure time physical activity was found with the lowest risk of IHD among nurses with the combination of moderate physical activity at work and vigorous physical activity during leisure time. Compared to this group high physical activity at work was associated with a higher risk of IHD at all levels of physical activity during leisure time increasing from hazard ratio 1.75 (95% confidence interval (CI) 1.10–2.80) among nurses with vigorous physical activity during leisure time to 2.65 (95% CI 1.44–4.88) among nurses being sedentary during leisure time.

Conclusions: This study among Danish nurses suggests that high physical activity at work is a risk factor for IHD among women. Vigorous physical activity during leisure time lowered but did not completely counteract the adverse effect of occupational physical activity on risk of IHD.

Keywords

Epidemiology, heart disease, occupational health, physical activity, prospective study, women

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Background

Work-related factors are known to contribute to the occurrence of ischaemic heart disease (IHD).[1,2] Studies among male workers have shown that high physical demands at work increase the risk of IHD and all-cause mortality and add to progression of sub-clinical carotid atherosclerosis.[3–8] Many female workers are still exposed to high physical demands at work,[9] but little is known about how this affects their risk of heart disease, as the few existing prospective studies show conflicting results.[4,10–15] The effect of high physical activity at work may differ between men

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and women due to gender differences in exposure[16] or in the physiological response to physical strain.[17]

It is well-documented that physical activity during leisure time decreases the risk of IHD and all-cause mortality.[18,19] Thus, physical activity at work and during leisure time seems to have contrasting health effects.[20] Leisure time physical activity has been shown to reduce the excessive risk for IHD mortality among men with physically demanding work in two Danish studies.[4,21] In contrast, a Belgian study found that men with both high physical activity at work and during leisure time had the highest risk of IHD.[7] The results among men are thus inconsistent, yet knowledge from studies among women is even more sparse on this matter. However, a recent Danish study indicated that both male and female workers would benefit from being physically active during leisure time irrespective of their level of physical activity at work.[22]

The aim of the study was to investigate physical activity at work and during leisure time in relation to risk of IHD among women in the Danish Nurse Cohort Study. It is our hypothesis that high physical activity at work increases the risk of IHD in contrast to a beneficial effect of vigorous leisure time physical activity. Further, we hypothesise that vigorous leisure time physical activity can moderate and thus counteract the increased risk of IHD associated with high physical activity at work.

Methods

Study population and exclusion criteria

The Danish Nurse Cohort Study was established in 1993 when all female members of the Danish Nurses' Association aged 45 years and over ($n = 23{,}170$) received a comprehensive self-administered questionnaire on health and lifestyle, including occupational status and working conditions. Almost all nurses in Denmark are members of the Danish Nurses Organization, and the coverage of female nurses is close to 100%. Overall, 19,898 women (86%) returned the questionnaire (23). Women who at baseline were not actively employed as nurses ($n = 7501$) or who at baseline had passed the retirement age, which in Denmark in 1993 was 65 years, ($n = 86$) were excluded from the study population. Based on register information, we excluded 105 women with a hospital admission from IHD prior to the baseline survey and two women who completed the questionnaire, but were registered in The Central Person Registry as emigrated or missing at baseline. Furthermore, women with missing information on physical activity at work and psychosocial work environment were excluded ($n = 111$). Thus, the study population was 12,093 women.

The Danish Ethics Committee for the City of Copenhagen and Frederiksberg approved the study (#01-103/93).

Measures of physical activity at work and leisure time physical activity

Physical activity at work was measured by the following question based on Saltin and Grimby:[24]

Which description most precisely covers your pattern of physical activity at work?

(i) Mainly sedentary (sedentary).
(ii) Work mainly carried out standing and walking (moderate).
(iii) Standing or walking work involving some lifting and carrying (demanding).
(iv) Heavy or fast and physically exerting work (strenuous).

The categories (iii) and (iv) were merged in most of the analyses and are referred to as 'high'. The question is in accordance with accelerometer data on overall activity.[25]

Physical activity during leisure time was also based on Saltin and Grimby:[24]

Which description most precisely covers your leisure time physical activity?

(i) Read, watch television or engaged in other sedentary activity (sedentary).
(ii) Go for a walk, use your bicycle, or perform light physical activity (moderate).
(iii) Are an active athlete or performing heavy gardening, house work etc. for at least four hours per week (high).
(iv) Vigorous training and participation in competitive sports several times a week (intensive).

The categories (iii) and (iv) were merged in the analysis and referred to as 'vigorous'. The question has acceptable validity.[26]

Covariates

Information on age was retrieved from the Central Person Registry. Covariates were all self-reported and collected at baseline through a questionnaire: family history of cardiac disease (female relatives with myocardial infarction before age 65 years), diabetes, body mass index (BMI) (weight in kg divided by square of height in m), smoking history, alcohol intake (beer, wine and spirits the last weekday and the previous weekend), work pressure, influence on the organisation

Table 1. Distribution of covariates according to level of physical activity at work for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2008.

Physical activity at work	Sedentary	Moderate	Demanding	Strenuous	*p*-Value
n	2.331	4.159	4.965	638	
Average age (years)	50.6	51.4	52.4	52.2	<0.001[a]
Predisposition IHD					
No	85.5	85.3	82.9	78.3	
Yes	5.4	5.9	5.9	4.7	<0.001[b]
Unknown	9.1	8.8	11.2	17.0	
Diabetes					
No	99.4	99.2	99.0	99.2	
Yes	0.6	0.8	1.0	0.8	0.22[b]
BMI					
Under 25	71.2	75.8	72.0	72.5	
25 ≤BMI <30	22.9	19.7	22.9	23.3	<0.001[b]
30 and above	5.9	4.5	5.1	4.2	
Smoking					
Never/former	62.5	63.6	60.6	49.5	<0.001[b]
Current	37.5	36.4	39.4	50.5	
Alcohol intake					
No alcohol intake	9.4	12.7	17.5	18.6	
1–28 U/wk	75.4	74.5	71.9	68.8	<0.001[b]
>28 U/wk	15.2	12.8	10.6	12.6	
Leisure time physical activity					
Vigorous	25.2	25.7	28.8	35.4	
Moderate	66.4	69.5	66.7	59.5	<0.001[b]
Sedentary	8.4	4.8	4.5	5.1	
Work pressure					
Suitable	35.4	44.5	38.1	11.1	
A little too high	46.7	44.2	49.1	48.3	
Much too high	16.4	10.2	12.0	40.4	<0.001[b]
A little/much too low	1.5	1.1	0.8	0.2	
Job influence					
Major influence	63.5	38.4	31.1	24	
Some influence	32.7	50.7	57.0	55.2	
Minor influence	2.9	9.3	10.4	16.1	<0.001[b]
No influence	0.9	1.6	1.5	4.7	
Shift work					
Day	90.1	69.7	43.9	37.1	
Evening	1.8	7.2	20.4	23.4	
Night	2.5	3.6	13.5	9.6	<0.001[b]
Rotate	5.6	19.5	22.2	29.9	
Working hours					
Per week					
1–36 h	18.6	47.6	63.9	59.3	
37–40 h	70.3	50.3	35.0	37.7	<0.001[b]
>40 h	11.1	2.1	1.1	3.0	

BMI: body mass index; IHD: ischaemic heart disease; [a]Kruskal-Wallis test; [b]Pearson chi^2 test.

of daily work, work hours per week and shift work. Categorisation of the covariates is shown in Table 1.

Endpoints

Subjects were censored when a first ever hospitalisation for IHD occurred (cases), or when they died, or were classified as emigrated or missing. Information on hospitalisation for a first ever IHD event was retrieved from the Danish National Patient Registry, which through a personal identification number registers all hospital admissions in Denmark. Information on date of death, and classification as emigrated or missing, was obtained from the Central Person Registry.

The National Patient Registry of Hospital Discharges is based on the International Classification of Diseases (ICD). IHD cases were defined as 410–414 in ICD-8 and I20–I25 in ICD-10. The follow-up for events was continued until 5 February 2008.

Statistical methods

The variables for physical activity at work and during leisure time were kept as categorical variables throughout the analysis. In the univariate analyses the Pearson chi-square test was used for categorical covariates and the Kruskal-Wallis test was used for continuous covariates. In the following analyses the two categories: 'demanding work' and 'strenuous work' were merged and referred to as 'high' but were analysed separately as well.

Cox proportional hazards models were used to test for association between IHD and physical activity at work, leisure time physical activity and covariates. Age was the underlying time scale, as recommended for outcomes where age is a stronger determinant of outcome than time-on study.[27] Age was implicitly adjusted for. In all Cox models 95% confidence intervals (CIs) were calculated. Data are presented with moderate physical activity at work as the reference group as both high physical activity at work[4] and high sitting time[28] may increase risk of cardiovascular disease. The interaction between physical activity at work and physical activity during leisure time was analysed in a stratified analysis with a common reference point. For this analysis a new variable was created with nine different combinations of sedentary, moderate and high/vigorous physical activity at work and during leisure time. Further, statistical interaction on a multiplicative scale was analysed by including a term of interaction in a separate analysis (Wald chi-square test).

We conducted a sensitivity analysis where nurses with poor or very poor self-rated health at baseline, which could be a marker for sub-clinical cardiovascular disease were excluded, and an analysis on the association between physical activity at work and all IHD diagnoses except angina pectoris (see Supplementary Tables).

In the Cox models, the proportional hazards assumption was evaluated for all variables by comparing estimated log-log survivor curves over the different categories of variables being investigated and by inspecting plots of Schoenfeld residuals.

Statistical analyses were performed using the statistical package Statistical Analysis System (SAS) version 9.3.

Results

The study included 12,093 female nurses who were actively employed in 1993. Their median age was 51 years. During the 15 years of follow-up, a total of 580 incident cases of IHD occurred. Among the 580 incident cases, 369 cases were angina pectoris, 138 were myocardial infarction and 73 were other IHD. Altogether 864 nurses died or were classified as emigrated or missing during follow-up. The average duration of follow-up was 14 years and the median duration 14.8 years (range 0.1–14.8 years). High physical activity at work was reported by 46.3% of the nurses, 34.4% had moderate physical activity at work and 19.3% were mainly sedentary at work. During leisure time 66.7% of the nurses were moderately active, 27.2% of the nurses were engaged in vigorous physical activity and 5.4% were mainly sedentary.

Table 1 presents all covariates according to level of physical activity at work. Among nurses with strenuous work, a higher percentage worked non-day shifts, reported much too high work pressure, minor or no job influence, were more often smokers, engaged in vigorous physical activity during leisure time and were unaware of familial predisposition to IHD compared to the other groups.

Table 2 shows in the age-adjusted model 1 that nurses who reported a high physical workload had around 40% higher risk of developing IHD compared to those with moderate physical activity at work. After inclusion of a number of traditional cardiovascular risk factors in model 2, the association between risk of IHD and high physical activity at work was slightly reduced, but remained significant. When leisure time physical activity was further included in model 3, the risk of IHD associated with high physical activity at work remained around 40%. In the final model 4 we further included work pressure, job influence, shift work and work hours per week. The risk of IHD associated with high physical activity at work was slightly lower (34%) but remained significant.

When an interaction term was introduced in a separate analysis, statistically significant interaction between physical activity at work and during leisure time was found ($p = 0.045$).

Table 2. The effect of including potential confounders on hazard ratio (HR) for ischaemic heart disease (IHD) according to physical activity at work and leisure time physical activity for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2008.

	Basic model 1[a,e]		Model 2[b,e]		Model 3[c,e]		Model 4[d,e]	
Characteristics	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Physical activity at work								
Sedentary	1.16	0.90–1.50	1.22	0.94–1.58	1.22	0.94–1.59	1.13	0.86–1.49
Moderate	1	–	1	–	1	–	1	–
High	1.42	1.17–1.72	1.37	1.12–1.67	1.38	1.12–1.68	1.34	1.08–1.66
Leisure time physical activity								
Sedentary	1.62	1.15–2.27	–	–	1.52	1.05–2.19	1.50	1.04–2.16
Moderate	1.10	0.91–1.33	–	–	1.18	0.96–1.45	1.12	0.96–1.45
Vigorous	1	–	–	–	1	–	1	–

BMI: body mass index; CI: confidence interval; [a]Model 1. Age as underlying time scale; [b]Model 2. Age as underlying time scale. Additionally adjusted for risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption); [c]Model 3. Further adjusted for leisure time physical activity; [d]Model 4. Further adjusted for work pressure, job influence, shift work and work hours per week; [e]The type 3 test for physical activity at work in the Cox models was: $p = 0.001$ in model 1, $p = 0.009$ in model 2, $p = 0.009$ in model 3 and $p = 0.026$ in model 4.

Table 3. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) by various combinations of different levels of physical activity at work and during leisure time for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2008.

				Basic model 1[a]		Model 2[b]	
Physical activity at work	Physical activity during leisure time	No with IHD	Total No	HR	95% CI	HR	95% CI
Sedentary	Sedentary	14	195	3.31	1.73–6.35	2.81	1.41–5.57
Sedentary	Moderate	54	1536	1.45	0.91–2.31	1.46	0.89–2.37
Sedentary	Vigorous	28	583	2.02	1.28–3.76	2.17	1.25–3.79
Moderate	Sedentary	8	199	1.56	0.71–3.45	1.45	0.62–3.37
Moderate	Moderate	125	2 871	1.70	1.11–2.59	1.71	1.10–2.66
Moderate	Vigorous	26	1063	1	–	1	–
High	Sedentary	22	255	3.30	1.87–5.82	2.65	1.44–4.88
High	Moderate	214	3662	2.15	1.43–3.22	2.09	1.36–3.21
High	Vigorous	85	1644	1.97	1.27–3.06	1.75	1.10–2.80

BMI: body mass index; [a]Model 1 age as underlying time scale; [b]Model 2 age as underlying time scale; Additionally adjusted for risk factors for IHD: Family history of IHD, diabetes, BMI, smoking and alcohol consumption and work pressure, job influence, work hours per week and shift work.

Table 3 presents the impact of combined exposure to physical activity at work and during leisure time on risk of IHD where the reference point chosen is the combination of moderate physical activity at work and vigorous physical activity during leisure time, giving the lowest risk. High physical activity at work was associated with increased risk of IHD in all three combinations with physical activity during leisure time, but with the highest risk among nurses being sedentary during leisure time and lowest among those with vigorous physical activity during leisure time, but the confidence intervals overlap. Sedentary work was associated with an increased risk of IHD among nurses being sedentary during leisure time and among nurses with vigorous leisure time physical activity (Table 3).

A sensitivity analysis showed that the effect was even stronger between high physical activity at work and myocardial infarction and other types of IHD apart from angina pectoris (see Supplementary Tables).

Another sensitivity analysis where nurses with poor or very poor self-rated health at baseline were excluded showed no indication of bias (see Supplementary Tables).

Discussion

This study among a large population of female nurses suggests that high physical activity at work is a risk factor for IHD among women. Nurses with high physical activity at work had an increased risk of IHD at all levels of physical activity during leisure time in spite of an interaction between physical activity at work and during leisure time.

In accordance with the suggested adverse effect of high physical activity at work among women in the present study, a case-control study from 2004 indicated that repetitive lifting and heavy lifting at work was associated with increased risk of MI among women, and a tendency of increased risk of MI was found among women with strenuous work.[10] In contrast, two other studies showed no association between occupational physical activity and all-cause mortality or myocardial infarction among women.[4,29] A Finnish study found that moderate and high physical activity at work decreased the risk of IHD among women[11] and in a Danish study a higher level of physical activity at work was associated with a lower mortality rate among women.[14]

However, most of the previous studies both among men and women are general population studies. The present study is unique in being conducted in a study population that is homogenous with respect to education and hence to a large extent socioeconomic status. This minimises confounding due to these factors. Physical activity at work is strongly associated with social class.[30] Residual confounding due to this factor may be a problem in general population cohorts and may partly explain some of the associations found in such studies. Similarly, lack of control for other important occupation risk factors such as shift work, work hours, job pressure and influence on work may have contributed to inconsistent results in the extant literature. To our knowledge this is the first study on occupational physical activity among women to account for these factors.

As expected, leisure time vigorous physical activity was associated with a decreased risk of IHD. We found a significant multiplicative interaction between occupational and leisure time physical activity. This means that the impact of physical activity at work on risk of IHD varied according to level of physical activity during leisure time. Nurses with vigorous physical activity during leisure time had a lower risk of IHD from high physical activity at work than those being sedentary during leisure time. However, high physical activity at work was still a risk factor for IHD even among those being most physically active during leisure time. In accordance with this finding a recent study among men indicated that the combination of high physical activity at work and during leisure time still is associated with an increased risk of IHD.[7] In contrast, a Danish study indicated that high physical activity during leisure time counteracted the adverse effects of high physical activity at work among men. Among women no significant interaction was found.[4] Recent studies indicate that demanding occupational physical activity does not have a significant training effect on the cardiovascular system.[3,25] It has been suggested that rather heavy and especially static work can cause overload[31] and that this overload of the cardiovascular system with a lack of time for restitution could account for the increased risk of IHD associated with physically demanding work[20] Lack of time for restitution could also be a possible explanation for the increased risk of IHD among nurses with the combination of physically demanding work and vigorous leisure time physical activity.

Compared to moderate physical activity during leisure time, both vigorous physical activity and being sedentary during leisure time may increase risk of IHD among nurses with sedentary work. Among nurses with moderate physical activity at work the highest risk of IHD was seen in the combination with moderate physical activity during leisure time. Though some of the differential interaction effects may be chance findings, future intervention studies are needed to investigate whether also vigorous physical activity during leisure time may have adverse effects on heart health and to evaluate effective and safe levels of physical activity during leisure time for persons at different levels of physical activity at work.

Strengths and weaknesses of the study

Strengths include the large cohort of women in a prospective design, high response rates, and a well known high validity of the self-reported information provided by the nurses.[32] Furthermore, information on incident and previous IHD was obtained through individual linkage to a nationwide hospital register. The follow-up was nearly complete apart from some of the cases suffering from less harmful heart diseases like angina pectoris. When treated in general practice they are not registered in the Danish National Patient Registry. This might have caused a small degree of non-differential misclassification, which may underestimate effects. However, the sensitivity analysis with myocardial infarction and other types of IHD apart from angina pectoris as outcome strengthens the result.

Exposure was measured only at one point in time. Furthermore the study had a rather long follow-up and some cohort members retired during follow-up and were no longer exposed to work factors. Though many of the nurses have been exposed to high physical activity during a long period of time, this may have caused some misclassification and reduced the strength of the association. The importance of duration and continuity of exposure is unknown and is important to explore in future studies.

Danish nurses tend to have a healthier lifestyle than other Danish women. However, findings based on the cohort can be generalised.[23] It is important though to further investigate the association between physical activity and IHD and the interplay with physical activity during leisure time in populations of women in general and to examine whether special circumstances exist in relation to the physical work demands of nurses.

Conclusion

The present study shows that high physical activity at work increases the risk of IHD in female nurses. To our knowledge this has not previously been demonstrated in a homogenous population of women.

Even though vigorous physical activity during leisure time was beneficial it did not completely counteract the increased risk of IHD associated with physically demanding work.

High physical activity at work should be considered a risk factor for IHD among female health care workers. More prospective studies in general populations and in other female professions are needed to elucidate whether high physical activity at work is a risk factor for IHD among women in general. Many women are still exposed to physically demanding jobs and this factor may be important to target in primary prevention.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Nurminen M and Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. *Scand J Work Environ Health* 2001; 27: 161–213.
2. Kivimaki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: A collaborative meta-analysis of individual participant data. *Lancet* 2012; 380: 1491–1497.
3. Holtermann A, Mortensen OS, Burr H, et al. Physical demands at work, physical fitness, and 30-year ischaemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 2010; 36: 357–365.
4. Holtermann A, Marott JL, Gyntelberg F, et al. Occupational and leisure time physical activity: Risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. *BMJ Open* 2012; 2: e000556.
5. Krause N, Brand RJ, Kaplan GA, et al. Occupational physical activity, energy expenditure and 11-year progression of carotid atherosclerosis. *Scand J Work Environ Health* 2007; 33: 405–424.
6. Holtermann A, Burr H, Hansen JV, et al. Occupational physical activity and mortality among Danish workers. *Int Arch Occup Environ Health* 2012; 85: 305–310.
7. Clays E, De BD, Janssens H, et al. The association between leisure time physical activity and coronary heart disease among men with different physical work demands: A prospective cohort study. *Eur J Epidemiol* 2013; 28: 241–247.
8. Kristal-Boneh E, Harari G, Melamed S, et al. Association of physical activity at work with mortality in Israeli industrial employees: The CORDIS study. *J Occup Environ Med* 2000; 42: 127–135.
9. Karlqvist LK, Harenstam A, Leijon O, et al. Excessive physical demands in modern worklife and characteristics of work and living conditions of persons at risk. *Scand J Work Environ Health* 2003; 29: 363–377.
10. Fransson E, De FU, Ahlbom A, et al. The risk of acute myocardial infarction: Interactions of types of physical activity. *Epidemiology* 2004; 15: 573–582.
11. Hu G, Jousilahti P, Borodulin K, et al. Occupational, commuting and leisure-time physical activity in relation to coronary heart disease among middle-aged Finnish men and women. *Atherosclerosis* 2007; 194: 490–497.
12. Salonen JT, Puska P and Tuomilehto J. Physical activity and risk of myocardial infarction, cerebral stroke and death: A longitudinal study in Eastern Finland. *Am J Epidemiol* 1982; 115: 526–537.
13. Lapidus L and Bengtsson C. Socioeconomic factors and physical activity in relation to cardiovascular disease and death. A 12 year follow up of participants in a population study of women in Gothenburg, Sweden. *Br Heart J* 1986; 55: 295–301.
14. Andersen LB, Schnohr P, Schroll M, et al. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med* 2000; 160: 1621–1628.
15. Petersen CB, Eriksen L, Tolstrup JS, et al. Occupational heavy lifting and risk of ischemic heart disease and all-cause mortality. *BMC Public Health* 2012; 12: 1070.
16. Aittomaki A, Lahelma E, Roos E, et al. Gender differences in the association of age with physical workload and functioning. *Occup Environ Med* 2005; 62: 95–100.
17. Aadahl M, von Huth SL, Pisinger C, et al. Five-year change in physical activity is associated with changes in cardiovascular disease risk factors: The Inter99 study. *Prev Med* 2009; 48: 326–331.
18. Samitz G, Egger M and Zwahlen M. Domains of physical activity and all-cause mortality: Systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol* 2011; 40: 1382–1400.

19. Vanhees L, De SJ, GeladaS N, et al. Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: Recommendations from the EACPR (Part I). *Eur J Prev Cardiol* 2012; 19: 670–686.
20. Krause N. Physical activity and cardiovascular mortality–disentangling the roles of work, fitness, and leisure. *Scand J Work Environ Health* 2010; 36: 349–355.
21. Holtermann A, Mortensen OS, Burr H, et al. The interplay between physical activity at work and during leisure time–risk of ischemic heart disease and all-cause mortality in middle-aged Caucasian men. *Scand J Work Environ Health* 2009; 35: 466–474.
22. Holtermann A, Marott JL, Gyntelberg F, et al. Does the benefit on survival from leisure time physical activity depend on physical activity at work? A prospective cohort study. *PLoS One* 2013; 8: e54548.
23. Hundrup YA, Simonsen MK, Jorgensen T, et al. Cohort profile: The Danish nurse cohort. *Int J Epidemiol* 2012; 41: 1241–1247.
24. Saltin B and Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. *Circulation* 1968; 38: 1104–1115.
25. Emaus A, Degerstrom J, Wilsgaard T, et al. Does a variation in self-reported physical activity reflect variation in objectively measured physical activity, resting heart rate, and physical fitness? Results from the Tromso study. *Scand J Public Health* 2010; 38: 105–118.
26. Kurtze N, Rangul V and Hustvedt BE. Reliability and validity of the international physical activity questionnaire in the Nord-Trondelag health study (HUNT) population of men. *BMC Med Res Methodol* 2008; 8: 63.
27. Korn EL, Graubard BI and Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. *Am J Epidemiol* 1997; 145: 72–80.
28. Katzmarzyk PT, Church TS, Craig CL, et al. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009; 41: 998–1005.
29. Wennberg P, Lindahl B, Hallmans G, et al. The effects of commuting activity and occupational and leisure time physical activity on risk of myocardial infarction. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 924–930.
30. Beenackers MA, Kamphuis CB, Giskes K, et al. Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: A systematic review. *Int J Behav Nutr Phys Act* 2012; 9: 116.
31. Ilmarinen J. Work and cardiovascular health: Viewpoint of occupational physiology. *Ann Med* 1989; 21: 209–214.
32. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986; 123: 894–900.

ARTICLE 2.

Allesøe K, Søgaard K, Aadahl M, Boyle E, Holtermann A.

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Are hypertensive women at additional risk of ischaemic heart disease from physically demanding work?

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Abstract

Background: The combination of hypertension and high physical activity at work may increase blood pressure considerably and increase the risk of atherosclerosis and thereby ischaemic heart disease (IHD), but only a few studies in men, and none among women, have examined this topic.

Design: This was a prospective cohort study.

Methods: In 1993, 12,093 female nurses from the Danish Nurse Cohort Study, aged 45–64 years answered a baseline questionnaire on physical activity at work, history of hypertension, a selection of known risk factors for IHD and occupational factors. Information on incident IHD from baseline to 2008 was retrieved by individual linkage to the National Register of Hospital Discharges.

Results: In a fully adjusted Cox model, hypertensive nurses with high physical activity at work had nearly three times higher risk of IHD (hazard ratio (HR) 2.87 (95% confidence interval (CI) 2.12–3.87)) compared to normotensive nurses with moderate physical activity at work. Significant additive interaction between physical activity at work and hypertension was found measured by the relative excess risk due to additive interaction (RERI) (1.20 (95% CI 0.26–2.14), and in an additive hazards model. Hypertensive nurses with high physical activity at work had 60 additional cases of IHD per 10,000 person years compared to normotensive nurses with moderate physical activity at work (60.0 (95% CI 38.1–81.9; $p < 0.001$)), of which more than half was explained by additive interaction (40.7 (95% CI 11.7–69.7; $p = 0.006$)). No multiplicative interaction ($p = 0.249$) was found.

Conclusions: This study among Danish nurses indicated that hypertensive women may be at particular high risk of IHD from physically demanding work.

Keywords

Heart disease, hypertension, occupational health, physical activity, prospective study, women

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Introduction

Recent studies, including a meta-analysis among male workers, have indicated that high physical demands at work increase the risk of ischaemic heart disease (IHD) and all-cause mortality, and also add to the progression of sub-clinical carotid atherosclerosis.[1–9] Among women, the evidence is sparse and inconsistent.[2,9–11] However, recent results from the Danish Nurse Cohort study found an increased risk of IHD from high physical activity at work.[12]

Physical demands at work such as lifting and carrying loads are known to cause a rise in cardiac output and to acutely elevate blood pressure.[13] Evidence from

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resistance training studies has shown that the blood pressure response can rise to excessive levels when carrying high loads.[14] Accordingly, studies suggest that static physical activity at work is associated with higher mean systolic blood pressure[15] and also heavy dynamic workload increases systolic blood pressure.[16] During prolonged hours of physically demanding work there may be repeated periods of elevated heart rate and blood pressure, which may increase unfavourable arterial flow patterns that are known to be associated with atherosclerosis.[17] As plaque formation in the arteries can also be induced by hypertension,[17] there may be interacting physiological mechanisms leading to progress of atherosclerosis. In addition, the combination of chronically elevated blood pressure in hypertensive individuals and repeated high peaks of blood pressure during a working day of physically demanding work may cause an overload or damage to the cardiovascular system.

Many male and female workers are still exposed to high physical demands at work[18] and the prevalence of hypertension is high in Europe and North America.[19] Therefore, the question whether hypertensive individuals are at particularly high risk of IHD when exposed to physically demanding work may be important in relation to occupational health prevention.

The aim of this study was to investigate the combined effect and the interaction of high physical activity at work and hypertension on the risk of IHD.

Methods

The design of the study was a prospective cohort study

Study population and exclusion criteria

The Danish Nurse Cohort Study was established in 1993 when all female members of the Danish Nurses' Association aged 45 years and above ($n = 23,170$) received a comprehensive self-administered questionnaire on health and lifestyle, including questions on occupational status and working conditions. Most nurses in Denmark are members of the Danish Nurses Association and the coverage of female nurses is close to 100%. Overall, 19,898 women (86%) returned the questionnaire.[20] Women who were not actively employed as nurses at baseline ($n = 7501$) or who had passed the retirement age ($n = 86$) (which at the time was 65 years) were excluded. Based on registry data, we excluded 105 women who had a hospital admission from IHD prior to the baseline survey and two women who completed the questionnaire but were registered as either having emigrated or as missing at baseline. Additionally, women with missing information on physical activity at work and psychosocial work environment were excluded ($n = 111$). Therefore, the study population was comprised of 12,093 women.

The Danish Ethics Committee for the City of Copenhagen and Frederiksberg approved the study (#01-103/93).

Measurement of physical activity at work and hypertension

Physical activity at work was measured by a four-class question first used in a study by Saltin and Grimby.[21] The four classes were: (a) mainly sedentary (sedentary), (b) mainly standing and walking but not physically exerting (moderate), (c) standing or walking which involves some lifting and carrying (demanding), (d) heavy or fast and physically exerting (strenuous). The categories (c) and (d) were merged in the majority of the analyses because of a small number in (d) and the merged category is referred to as 'high'.

Hypertension was self-reported through answering yes or no to a single question: 'Are you now or have you previously been suffering from hypertension?'.

Covariates

Information on age was retrieved from the Central Person Registry, which contains basic personal information on all residents in Denmark identified by a personal identification number. The following covariates were all self-reported and collected at baseline: family history of cardiac disease (female relatives with myocardial infarction (MI) before age 65 years); diabetes; body mass index (BMI) (kg/m^2); leisure time physical activity;[21] smoking history; alcohol intake; use of anti-hypertensive medication during the previous two weeks; work pressure; influence on the organisation of daily work; work hours per week; and doing shift work. Categorisation of the covariates is shown in Table 1.

Endpoints

Subjects were censored when they were first-ever hospitalised for IHD (cases), when they died, or were classified as emigrated or missing. Information on hospitalisation for a first-ever IHD event was retrieved from the Danish National Patient Registry, which through a personal identification number registers all hospital admissions in Denmark and is based on the International Classification of Diseases (ICD). IHD cases were defined as 410–414 in ICD-8 and I20–I25 in ICD-10. Information on dates of death, classification as emigrated or missing was obtained from the Central Person Registry. The nurses were followed till 5 February 2008.

Table 1. Distribution of covariates (%) according to hypertension status of 12,093[a] female nurses from the Danish Nurse Cohort Study, 1993–2008.

	Normotensive	Hypertensive	
	n = 10,638	n = 1400	p-Value[b]
Age in years			
45–49	42.3	27.2	<0.001
50–54	28.2	29.6	
55–59	23.1	34.6	
60–64	6.4	8.6	
Physical activity at work			
Sedentary	19.3	19.2	0.367
Moderate	34.7	32.5	
Demanding	40.7	42.9	
Strenuous	5.3	5.4	
Civil status			
Married/cohabiting	80.4	81.0	0.597
Single	19.6	19.0	
Predisposition IHD			
No	84.4	81.3	0.008
Yes	5.6	7.2	
Unknown	10.0	11.5	
Diabetes			
No	99.3	97.6	<0.001
Yes	0.7	2.4	
BMI (kg/m^2)			
BMI < 25	75.4	56.5	<0.001
25 ≤ BMI < 30	20.5	31.2	
30 and above	4.1	12.3	
Smoking			
Never/former	60.7	66.8	<0.001
Current	39.3	33.2	
Alcohol intake			
No alcohol intake	14.2	15.8	0.030
1–28 units/week	73.7	70.3	
>28 units/week	12.1	13.9	
Leisure time physical activity			
Vigorous	28.0	23.0	<0.001
Moderate	66.9	69.5	
Sedentary	5.1	7.5	
Work pressure			
Suitable	38.6	36.0	<0.039
A little too high	46.8	48.0	
Much too high	13.6	15.4	
A little/much too low	1.0	0.6	
Job influence			
Major influence	39.8	37.7	0.270
Some influence	49.7	52.0	
Minor/no influence	10.5	10.3	
Shift work			
Day	61.1	63.4	0.047
Evening	12.4	12.3	
Night	7.6	8.4	
Rotate	18.9	15.9	

(continued)

Table 1. Continued

	Normotensive	Hypertensive	
	n = 10,638	n = 1400	p-Value[b]
Working hours per week			
<40	96.5	96.3	0.619
>40	3.5	3.7	

BMI: body mass index; IHD: ischaemic heart disease.
[a]Missing information on hypertension for 55 persons
[b]Pearson chi-squared test.

Statistical methods

In the bivariate analysis, the level of physical activity at work and covariates by hypertension status were measured as frequencies (%) and tested by use of the Pearson chi-square test.

The Cox proportional hazards models were used to test for association between IHD and physical activity at work, hypertension and the covariates. Age was the underlying timescale as recommended for outcomes where age is a stronger determinant of outcome than time in the study,[22] and thus age was adjusted implicitly. In all Cox models, 95% confidence intervals (CIs) were calculated. Data are presented with the combination of normal blood pressure and moderate physical activity at work as the reference group. Moderate physical activity at work was chosen for reference purposes as both high physical activity at work[6] and high sitting time[23] have been shown to increase the risk of cardiovascular disease. The covariates considered a priori as potential confounders were included in the adjusted analyses. For all covariates, the category anticipated to pose the lowest risk of IHD was chosen as the reference category.

In the Cox models, the proportional hazards assumption was evaluated for all variables by comparing estimated log-log survivor curves over the different categories of variables being investigated and by inspecting plots of Schoenfeld residuals.

The interaction between physical activity at work and hypertension was first analysed as the departure from multiplicativity by including a term of interaction in a Cox model (tested by Wald chi-square test). Secondly, we investigated additive interaction in the same multiplicative model by calculating relative excess risk due to additive interaction (RERI) and the corresponding 95% CI based on the method for categorical variables with two or more levels.[24] Thirdly, we investigated interaction and calculated the number of additional incident cases of ischaemic heart disease per person year compared to normotensive nurses with moderate physical activity at work in an additive hazards model.[25]

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to interplay between hypertension and physical activity at work (OPA) for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2008.

		Basic model 1[a]		Model 2[b]	
Combination of OPA and hypertension	*n*/Number with IHD	HR	95% CI	HR	95% CI
Normotensive-moderate OPA	3691/130	1		1	
Normotensive-high OPA	4893/235	1.29	1.04–1.60	1.21	0.95–1.53
Normotensive-sedentary OPA	2054/71	1.06	0.79–1.42	1.04	0.77–1.42
Hypertensive-moderate OPA	455/30	1.75	1.17–2.60	1.56	1.01–2.39
Hypertensive-high OPA	676/85	3.20	2.43–4.21	2.87	2.12–3.87
Hypertensive-sedentary OPA	269/25	2.57	1.67–3.94	2.33	1.48–3.67

BMI: body mass index.
Sample size is given by *n*.
[a]Model 1 age as underlying timescale including a term of interaction (OPA × hypertension).
[b]Model 2 age as underlying timescale including a term of interaction (OPA × hypertension). Additionally adjusted for traditional risk factors for IHD: family history of IHD, diabetes, BMI, smoking, alcohol consumption, physical activity during leisure time and for work pressure, job influence, work hours per week and shift work.

We conducted sensitivity analyses separately among hypertensive nurses using anti-hypertensive medication and among hypertensive nurses not using anti-hypertensive medication.

All statistical analyses were performed using the statistical package SAS version 9.3.

Results

During the 15 years of follow-up, a total of 580 incident cases of IHD occurred. These were comprised of 369 (63.6%) cases of angina pectoris, 138 (23.8%) cases of MI and 73 (12.6%) other forms of IHD. During follow-up, 864 (7.1%) nurses died, emigrated or were classified as missing. The average length of follow-up was 14 years and the median length was 14.8 years (range 0.1–14.8 years).

High physical activity at work was reported by 46.3% of the nurses, 34.4% had moderate physical activity at work and 19.3% were mainly sedentary at work. Nearly 12% (1400) of the nurses reported having hypertension. The proportion with hypertension was not significantly different according to level of physical activity at work.

Compared to normotensive nurses, a significantly higher percentage of the hypertensive nurses were engaged in moderate and sedentary leisure time physical activity, had diabetes, had familial predisposition to IHD, had BMI above 25, had high work pressure, worked the day shift and were older. Fewer of the hypertensive nurses were smokers (Table 1).

Nurses with hypertension had more than twice the risk of IHD compared to normotensive nurses in the fully adjusted model (hazard ratio (HR) 2.12 (95% CI 1.72–2.61)). Nurses with high physical activity at work had 34% higher risk of developing IHD compared to those with moderate physical activity at work in the fully adjusted model (HR 1.34 (95% CI 1.08–1.66)). Inclusion of hypertension as a covariate in this model had a minor effect on the estimate (HR 1.32 (95% CI 1.07–1.64)).

Table 2 presents the impact of the combined exposure to physical activity at work and hypertension on the risk of IHD where the reference point was the combination of moderate physical activity at work and normal blood pressure at baseline. In the basic age-adjusted analysis, high physical activity at work was predictive of an increased risk of IHD in both the normotensive and hypertensive nurses. In the fully adjusted model, hypertensive nurses with high physical activity at work had a significantly and nearly three times higher risk of IHD than normotensive nurses with moderate physical activity at work. In normotensive women with high physical activity at work, the risk of IHD was no longer significantly increased compared to normotensive women with moderate physical activity at work.

The combination of sedentary work and hypertension was also associated with higher risk of IHD compared to normotensive nurses with moderate physical activity at work. Among normotensive nurses, sedentary work was not associated with increased risk of IHD compared to moderate physical activity at work (Table 2).

In an analysis of the effect of physical activity at work on risk of IHD in strata according to the presence or absence of hypertension at baseline with separate reference points, the association between high physical activity at work and IHD showed the same trend as in Table 2 both among hypertensive and normotensive nurses (data not shown).

Measures of multiplicative and additive interaction

When an interaction term between physical activity at work and hypertension was introduced in the fully

Table 3. Additive hazards model. Estimation of absolute size of the additional numbers of cases of incident ischaemic heart disease (IHD) due to the combined effect of hypertension and physical activity at work (OPA) for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2008.

		Basic model 1[a]		Model 2[b]	
	n/Number with IHD	Additional cases/10,000 person years	95% CI (*p*-value)	Additional cases/10,000 person years	95% CI (*p*-value)
Normotensive-moderate OPA	3691/130	1		1	
Normotensive-high OPA	4893/235	7.1	1.0–13.3 (0.023)	4.5	–2.4–11.3 (0.200)
Normotensive-sedentary OPA	2054/71	2.0	–5.1–9.1 (0.585)	0.7	–7.2–8.5 (0.862)
Hypertensive-moderate OPA	455/30	19.7	2.4–37.3 (0.028)	14.9	–4.1–33.8 (0.124)
Hypertensive-high OPA	676/85	63.3	42.5–84.1 (<0.001)	60.0	38.1–81.9 (<0.001)
Hypertensive-sedentary OPA	269/25	41.2	16.8–65.6 (<0.001)	39.0	10.8–67.2 (0.006)
Additive interaction hypertension-high OPA		36.5	9.2–63.7 (0.009)	40.7	11.7–69.7 (0.006)
Additive interaction hypertension-sedentary OPA		19.5	–10.2–49.2 (0.198)	23.5	–10.4–57.3 (0.174)

BMI: body mass index; CI: confidence interval; HR: hazard ratio.
The sample size is given by *n*.
[a]Model 1 age as underlying timescale
[b]model 2 age as underlying timescale, additionally adjusted for traditional risk factors for IHD: family history of IHD, diabetes, BMI, smoking, alcohol consumption, physical activity during leisure time and for work pressure, job influence, work hours per week and shift work.

adjusted Cox model in Table 2, no significant multiplicative interaction was found ($p = 0.249$). However, significant additive interaction was found by the RERI measure due to additive interaction where a value above zero is a sign of interaction. In the age-adjusted analysis, RERI was: 1.17 (95% CI 0.22–2.12) and in the fully adjusted model RERI was: 1.20 (95% CI 0.26–2.14).

An additive hazards model showed significant additive interaction between high physical activity at work and hypertension. Table 3 shows the number of additional cases of IHD per 10,000 person years associated with the combinations of hypertension and levels of physical activity at work compared to the number of cases among normotensive nurses with moderate physical activity at work. Nurses with high physical activity at work and hypertension had 60 additional cases of IHD per 10,000 person years compared to normotensive nurses with moderate physical activity at work in the fully adjusted model (Table 3). Out of these 60 additional cases, around 40 and thus more than half of the additional cases of IHD were explained by additive interaction between high physical activity at work and hypertension (Table 3). There was no significant additive interaction between sedentary work and hypertension (Table 3).

Sensitivity analyses

We performed a sensitivity analysis among 654 nurses who reported hypertension and not using anti-hypertensive medication. In the fully adjusted model, nurses with high physical activity at work had a marginally significant and more than twice as high risk of IHD than those with moderate occupational physical activity (HR 2.06 (95% CI 0.97–4.41)). The result of the corresponding analysis among 721 nurses who reported both having hypertension and use of anti-hypertensive medication was (HR 1.87 (95% CI 1.02–3.44)).

Discussion

This study examined the combined and interaction effects of high physical activity at work and hypertension on the 15-year risk of IHD in a large cohort of female nurses. The main findings were that nurses with hypertension and high physical activity at work had nearly three times higher risk of IHD compared to normotensive nurses with moderate physical activity at work. Among normotensive nurses with high physical activity at work, the corresponding risk of IHD was small and insignificant in the fully adjusted model. Further, a significant additive interaction between high physical activity at work and hypertension was found, which suggests that more than half of the additional cases of IHD among nurses with high physical activity at work and hypertension are due to the additive interaction between the two exposures. This implies that physically demanding work may be especially detrimental for hypertensive women. To our knowledge, this has not previously been shown among women.

Among men, one study found that hypertensive men with high physical workload had a significantly higher risk of IHD compared to normotensive men with low physical workload, but only among those with an increased blood pressure during follow-up.[16] In contrast, a Danish study found high physical work demands to be associated with higher risk for IHD and all-cause mortality only among normotensive men, and not among those with hypertension; however, without reporting interaction effects.[26]

Physically demanding work may cause a rise in the cardiac output and blood pressure[13,27] and may be carried out for many hours every workday. A long-term elevated heart rate during work increases the time within the systolic cardiac phases, where unfavourable flow patterns known to be associated with plaque formation are most frequent which may over time cause atherosclerosis.[17] These possible plaque formation processes in the arteries may be further potentiated by the chronically elevated blood pressure in hypertensive individuals, as hypertension is known to cause atherosclerosis possibly in interaction with other risk factors.[17] Atherosclerosis may therefore potentially be an underlying mechanism behind the association between physically demanding work and IHD[3] as well as behind the interaction effect between high physical work load and hypertension.

Peak pressures during strenuous work tasks as heavy lifting may as well add to and worsen the many detrimental effects of hypertension. Knowledge from studies on resistance exercise has shown that during heavy lifting extremely high blood pressure elevations to above 300/200 mm Hg can occur.[14] The resulting sudden change in pressure may cause further stress on the arterial walls, which is speculated to be one of the causes of ruptures in plaques.[17] Even though the load during strenuous nursing work is much lower than during resistance exercise, it is likely that lifting heavy burdens at work could be associated with considerable high peaks in blood pressure.

In our study, hypertensive nurses with sedentary work had more than twice the risk of IHD compared to normotensive nurses with moderate physical activity at work and this may be interesting to investigate in future studies.

Furthermore, the present results calls for future studies with more statistical power to answer the question as to whether normotensive women with high physical activity at work have an increased risk of IHD

Strengths and weaknesses of the study

This study used a large cohort of women in a prospective design and had high response rates. Furthermore, information on incident and previous IHD was obtained through individual linkage to a nationwide hospital register, with complete coverage and the follow-up was nearly complete. Sensitivity analyses were performed to take potential sources of bias into account, as described in a previous study.[12]

The study population is homogenous and therefore confounding due to sex, education and to a large extent socioeconomic status is minimised. Though the study only covers one profession, which affects the external validity, a study comparing Danish nurses with the general female population concluded that findings based on the cohort can be generalised.[20]

Hypertension as well as physical activity at work and all covariates were self-reported. This could result in some degree of nondifferential misclassification, which will tend to dilute associations. However, self-reported information provided by nurses is known to have a high validity,[28] and due to their professional skills they are likely to be well qualified to assess medical conditions. The question concerning physical activity at work was shown to be in accordance with accelerometer data on overall activity.[29]

As one of few studies we have adjusted for occupational risk factors such as shift work, work hours, job pressure and influence on work, which could be important confounders.

It is not known whether hypertension may be in the causal pathway between physical activity at work and IHD. However, in a separate analysis with adjustment for hypertension at baseline the association between high physical activity at work and IHD was only slightly changed, and hence a considerable mediating effect of hypertension at baseline is not likely.

Conclusions

The present study among Danish nurses suggests that hypertensive women are at particular risk of IHD when exposed to high physical activity at work. Hypertensive nurses with high physical activity at work had nearly three times higher risk of IHD compared to normotensive nurses exposed to moderate physical activity at work. An additive hazards model showed that more than half of the additional cases of IHD among hypertensive nurses with high physical activity at work compared to normotensive nurses with moderate physical activity at work can be explained by the significant additive interaction of the two exposures. To our knowledge, this has not previously been demonstrated among women.

If the finding that hypertensive nurses have an excessive risk of IHD from exposure to physically demanding work is confirmed in future epidemiological studies, it ought to be incorporated in occupational health counselling and job modification for hypertensive women.

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Declaration of conflicting interests

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References

1. Holtermann A, Mortensen OS, Burr H, et al. Physical demands at work, physical fitness, and 30-year ischaemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 2010; 36: 357–365.
2. Holtermann A, Marott JL, Gyntelberg F, et al. Occupational and leisure time physical activity: Risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. *BMJ Open* 2012; 2: e000556.
3. Krause N, Brand RJ, Kaplan GA, et al. Occupational physical activity, energy expenditure and 11-year progression of carotid atherosclerosis. *Scand J Work Environ Health* 2007; 33: 405–424.
4. Holtermann A, Burr H, Hansen JV, et al. Occupational physical activity and mortality among Danish workers. *Int Arch Occup Environ Health* 2012; 85: 305–310.
5. Clays E, De Bacquer D, Janssens H, et al. The association between leisure time physical activity and coronary heart disease among men with different physical work demands: A prospective cohort study. *Eur J Epidemiol* 2013; 28: 241–247.
6. Li J, Loerbroks A and Angerer P. Physical activity and risk of cardiovascular disease: What does the new epidemiological evidence show? *Curr Opin Cardiol* 2013; 28: 575–583.
7. Krause N, Brand RJ, Arah OA, et al. Occupational physical activity and 20-year incidence of acute myocardial infarction: Results from the Kuopio Ischemic Heart Disease Risk Factor Study. *Scand J Work Environ Health* 2014; 41: 124–139.
8. Harari G, Green MS and Zelber-Sagi S. Combined association of occupational and leisure-time physical activity with all-cause and coronary heart disease mortality among a cohort of men followed-up for 22 years. *Occup Environ Med* 2015; 72: 617–624.
9. Hu GC, Chien KL, Hsieh SF, et al. Occupational versus leisure-time physical activity in reducing cardiovascular risks and mortality among ethnic Chinese adults in Taiwan. *Asia Pac J Public Health* 2014; 26: 604–613.
10. Hu G, Jousilahti P, Borodulin K, et al. Occupational, commuting and leisure-time physical activity in relation to coronary heart disease among middle-aged Finnish men and women. *Atherosclerosis* 2007; 194: 490–497.
11. Andersen LB, Schnohr P, Schroll M, et al. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med* 2000; 160: 1621–1628.
12. Allesoe K, Holtermann A, Aadahl M, et al. High occupational physical activity and risk of ischaemic heart disease in women: The interplay with physical activity during leisure time. *Eur J Prev Cardiol* 2015; 22: 1601–1608.
13. Åstrand P, Rodahl K, Dahl H, et al. *Textbook of work physiology*. 4th ed. Champaign, IL, USA: Human Kinetics, 2003.
14. MacDougall JD, Tuxen D, Sale DG, et al. Arterial blood pressure response to heavy resistance exercise. *J Appl Physiol* 1985; 58: 785–790.
15. Clays E, De Bacquer D, Van Herck K, et al. Occupational and leisure time physical activity in contrasting relation to ambulatory blood pressure. *BMC Public Health* 2012; 12: 1002.
16. Virkkunen H, Harma M, Kauppinen T, et al. Shift work, occupational noise and physical workload with ensuing development of blood pressure and their joint effect on the risk of coronary heart disease. *Scand J Work Environ Health* 2007; 33: 425–434.
17. Glagov S, Zarins C, Giddens DP, et al. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* 1988; 112: 1018–1031.
18. Karlqvist LK, Harenstam A, Leijon O, et al. Excessive physical demands in modern worklife and characteristics of work and living conditions of persons at risk. *Scand J Work Environ Health* 2003; 29: 363–377.
19. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003; 289: 2363–2369.
20. Hundrup YA, Simonsen MK, Jorgensen T, et al. Cohort profile: The Danish nurse cohort. *Int J Epidemiol* 2012; 41: 1241–1247.
21. Saltin B and Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. *Circulation* 1968; 38: 1104–1115.
22. Korn EL, Graubard BI and Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. *Am J Epidemiol* 1997; 145: 72–80.
23. Katzmarzyk PT, Church TS, Craig CL, et al. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009; 41: 998–1005.
24. Li R and Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol* 2007; 17: 227–236.
25. Rod NH, Lange T, Andersen I, et al. Additive interaction in survival analysis: Use of the additive hazards model. *Epidemiology* 2012; 23: 733–737.
26. Holtermann A, Mortensen OS, Burr H, et al. Physical work demands, hypertension status, and risk of ischemic

heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 2010; 36: 466–472.
27. Korshoj M, Clays E, Lidegaard M, et al. Is aerobic workload positively related to ambulatory blood pressure? A cross-sectional field study among cleaners. *Eur J Appl Physiol* 2015. Epub ahead of print 12 September 2015. DOI: 10.1007/s00421-015-3259-9.
28. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986; 123: 894–900.
29. Emaus A, Degerstrom J, Wilsgaard T, et al. Does a variation in self-reported physical activity reflect variation in objectively measured physical activity, resting heart rate, and physical fitness? Results from the Tromso study. *Scand J Public Health* 2010; 38: 105–118.

ARTICLE 3.

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Does influence at work modify the relation between high occupational physical activity and risk of heart disease in women?

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ORIGINAL ARTICLE

Does influence at work modify the relation between high occupational physical activity and risk of heart disease in women?

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Abstract

Purpose To investigate whether influence at work modifies the association between demanding and strenuous occupational physical activity (OPA) and risk of ischaemic heart disease (IHD).

Methods A sample of 12,093 nurses aged 45–64 years from the Danish Nurse Cohort Study was followed for 20.6 years by individual linkage to incident IHD in the Danish National Patient Registry. Information on OPA, influence at work, other occupational factors and known risk factors for IHD was collected by self-report in 1993.

Results During follow-up 869 nurses were hospitalised with incident IHD. Nurses exposed to strenuous OPA and low influence at work had a 46% increased risk of IHD [hazard ratio (HR) 1.46 (95% confidence interval (CI) 1.02–2.09)] compared to the reference group of nurses with moderate OPA and high influence at work. Nurses exposed to strenuous OPA and high influence at work were not at an increased risk of IHD [HR 1.10 (95% CI 0.59–2.06)]. An additive hazards model showed there were 18.0 (95% CI −0.01 to 36.0) additional cases of IHD per 10,000 person years among nurses with strenuous OPA and low influence at work compared to nurses with moderate OPA and high influence at work. A detrimental additive interaction between strenuous OPA and low influence at work that could explain the additional cases of IHD among nurses with strenuous OPA and low influence at work was indicated.

Conclusion The findings suggest that high influence at work may buffer some of the adverse effects of strenuous OPA on risk of IHD.

Keywords Heart disease · Occupational health · Physical activity · Influence at work · Prospective study · Women

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Introduction

Cardiovascular disease (CVD) is the leading cause of death among adult women in all European countries (Nichols et al. 2012). It is also the most common cause of death for adult women in the United States (Mosca et al. 2011).

High occupational physical activity (OPA) has been associated with an increased risk of CVD (Li et al. 2013) and all-cause mortality (Harari et al. 2015; Holtermann et al. 2012a, b; Hu et al. 2014) in recent studies among men. Among women, some of the recent studies have shown no effect of high OPA on risk for all-cause mortality or CVD (Holtermann et al. 2012a, b; Richard et al. 2015). However, a recent Danish study among female nurses showed that high OPA was associated with an increased risk of IHD (Allesoe et al. 2015) and in two other studies, a detrimental association between high

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OPA and IHD (Petersen et al. 2012) and CVD (Hu et al. 2014) was indicated.

Many European workers are exposed to high physical work demands. Exposure levels for women are in general lower than for men except for lifting and moving people, and repetitive movements (Eurofound 2015). Work in many occupations involves high physical demands where the metabolic demands exceed the recommended limit for an eight hour work day of one third of the individual's maximal aerobic capacity and this could result in a risk of overload (Karlqvist et al. 2003). In Denmark, the percentage of nurses with demanding or strenuous work is higher than the average for female Danish workers (Det Nationale Forskningscenter for Arbejdsmiljø 2010). Furthermore, on average 7–10% of the nurses have to push, pull or carry heavy burdens more than half of their working time and this percentage is higher among nurses at some wards, e.g. emergency, medical and surgery wards (Sørensen 2017; Wethje and Borg 2006).

The detrimental effect of high OPA on health could be explained by some of the characteristics of OPA, e.g. that at work, physical activity is carried out for many hours during the working day and for some workers with limited opportunities for breaks when needed. For workers with high OPA, the possibility to organize their work and thus the ability to take rests between strenuous tasks may be especially important (Holtermann 2015). This implies that influence at work could be an important factor in prevention of health hazards in physically strenuous jobs. The Demand-Control model developed by Karasek and Theorell (1990) proposes that in particular the joint exposure to both high psychological demands and low control (called job strain) is a health hazard. This hypothesis has been examined in numerous epidemiological studies and two recent meta-analyses indicated that job strain was associated with about 23% (Kivimaki et al. 2012) to 33% (Kivimaki and Kawachi 2015) increased risk of IHD. The mechanisms through which job strain may affect cardiovascular health are not well understood. It has been suggested and controversially discussed whether high job control—by enabling the possibility to cope with and handle the high psychological demands—may buffer and thus protect against detrimental health effects of high psychosocial demands such as time pressure, quantitative demands end conflicting demands (Hallqvist et al. 1998; Häusser et al. 2010; Karasek and Theorell 1990; Kasl 1996). There could be a similar buffering effect of high job control or aspects of job control as, e.g. the ability to plan and organise one's work in relation to the impact on health of high OPA. However, only one previous study among men investigating whether high job control has a buffering effect on the risk of heart disease from exposure to high OPA (Clays et al. 2016) has been identified. There have to our knowledge been no published studies examining this issue in women.

The aim of the present study was to investigate whether influence at work modifies the association between demanding and strenuous OPA and risk of IHD in female nurses. Our hypothesis was that having high influence on the organisation of the daily work could counteract a detrimental relation between demanding and strenuous OPA and risk of IHD.

Methods

Study population

The study design was a prospective cohort study. The study was based on data from the Danish Nurse Cohort Study, which was composed of female members from the Danish Nurses Association aged 45 years and older at baseline. In 1993, 23,170 nurses were invited to participate and 19,898 (86%) answered a questionnaire on health, lifestyle, occupational status and working conditions (Hundrup et al. 2012). We included nurses, who at baseline in 1993 were aged 45–64 years, were registered as citizens in Denmark, were actively employed as nurses, did not have prior hospital admission for IHD and had completed the self-report questions on OPA and psychosocial work factors. A total of 12,093 nurses were included in the analyses.

The Danish Ethics Committee for the cities of Copenhagen and Frederiksberg approved the study (#01-103/93).

Exposure measures

OPA was assessed by a four class question based on Saltin and Grimby's OPA question (Saltin and Grimby 1968). The OPA question was: "Which description most precisely covers your pattern of physical activity at work?" (i) Mainly sedentary work without any physical exertion (sedentary OPA), (ii) work that to a large extent is carried out standing or walking, but is otherwise not physically exerting (moderate OPA), (iii) standing or walking work that involves some lifting or carrying (demanding OPA), (iv) heavy or fast and physically exerting work (strenuous OPA).

Influence at work was assessed by a single item: "what level of influence do you normally have on the organisation of your daily work?" (i) high influence, (ii) some influence, (iii) very low influence, (iv) no influence. We dichotomised the variable into the categories of "high" [category (i)] and "low" influence at work [the categories (ii, iii and iv)] in some of the analyses.

Covariates

Information for the covariates was from the 1993 self-report questionnaire except for age, which was retrieved from the Central Person Registry. This registry contains basic personal information on all residents in Denmark. The covariates we included in the fully adjusted models were the following: age, body mass index (BMI) [weight (kg)/(height (m))^2], family history of cardiac disease (female relatives with myocardial infarction before age 65), diabetes (yes or no), smoking history (never, former and current), alcohol intake beer, wine and spirits consumed in the last weekday and in the previous weekend [no alcohol intake, 1–14, 15–21, >21 Units of alcohol (U)/week (Wk.) (U/Wk.)], total number of work hours per week, work pressure (much or a little too low, suitable, a little too high, much too high) and shift work (day, evening, night, rotate).

Endpoints

Using a personal identification number, the nurses were followed in two registries (The Danish National Patient Registry and the Danish Central Person Registry) for a total of 20.6 years starting from 1993 until November 2013. The outcome in this study was first ever hospitalisation with IHD according to the Danish National Patient Registry. IHD cases were defined as hospitalisation for myocardial infarction (ICD-8: 410 or ICD-10: I21–23), other acute or chronic IHD (ICD-8: 411 or 412 or ICD-10: I24 or I25), angina (ICD-8: 413 or ICD-10: I20) or electrocardiographically diagnosed heart disease (ICD-8: 414).

Nurses were censored as cases when they had an event (first ever hospitalisation with IHD). Otherwise, they were censored when they died out of hospital from all causes, when they died in hospital from causes other than IHD, when they emigrated or at the end of the follow-up period. The censoring dates for death or emigration were retrieved from the Central Person Registry.

Statistical methods

The distribution of the level of OPA, influence at work and covariates in the study population and the frequency of cases of IHD at each level of all variables were calculated as percentages.

We used Cox proportional hazards (PH) models to test for the associations between IHD and OPA and influence at work. Age was the underlying time scale for the analyses, and therefore, age was adjusted for implicitly. It is recommended to use age as the time scale when it is a stronger determinant of the outcome than the time in the study (Korn et al. 1997). In all Cox PH models, 95% confidence intervals (CI) were calculated. The available covariates considered a priori as potential confounders for the association between OPA and IHD, as well as for the association between influence at work and IHD were included in the adjusted analyses. We considered confounding control for both associations to be able to identify a susceptible subgroup and to identify whether an intervention targeted at increasing influence at work could prevent IHD as recommended by VanderWeele and Knol (2014). Work pressure was associated with both OPA and influence at work and was, therefore, not included in the fully adjusted analyses of the joint effect of OPA and influence at work. Instead, sensitivity analyses were performed where work pressure was further adjusted for and where possible interaction between work pressure, OPA and influence at work was investigated. For all exposure variables and covariates the category anticipated to pose the lowest risk of IHD was chosen as the reference.

In the Cox PH models, the proportional hazards assumption was evaluated for all variables by comparing estimated log–log survivor curves over the different categories of variables being investigated and by inspecting plots of Schoenfeld residuals.

Interaction between OPA and influence at work was tested as departure from multiplicativity by including a term of interaction in a Cox PH model tested by the Wald Chi-square test. The result from this model is presented first with a common reference group (moderate OPA and high influence at work) and second as the effect of OPA on risk of IHD within strata of influence at work. We further investigated the interaction by calculating the number of additional incident cases of IHD per 10,000 person years compared to nurses with moderate OPA and high influence at work in an additive hazards model (Rod et al. 2012).

In a sensitivity analysis, nurses were censored when they became 70 years old if they were not censored prior to this time.

In all analyses, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the statistical package SAS version 9.3 and R 64 3.2.2.

Results

During follow-up, a total of 869 incident cases of IHD occurred. Out of these, there were 494 (56.9%) cases of angina, 232 (26.7%) cases of myocardial infarction and 143 (16.4%) other forms of IHD. Apart from these cases, 1469 (12.2%) of the nurses were censored at the time of death or the time of emigration. The average length of follow-up was 19.0 years and the median length was 20.6 years (range 0.1–20.6 years).

Table 1 shows the categorisation and distribution of OPA, influence at work and the covariates for all nurses

Table 1 Distribution of physical activity at work, influence at work and covariates (number and percentages) and number and frequency of incident cases of ischeamic heart disease (IHD) among 12,093 female nurses from the Danish Nurse Cohort Study

	Participants		IHD cases	
	N	%[a]	*n*	%[b]
Age (years)				
45–49	4898	40.5	238	4.9
50–54	3427	28.3	235	6.9
55–59	2966	24.5	300	10.1
60–64	802	6.6	96	12.0
Physical activity at work				
Sedentary	2331	19.2	139	6.0
Moderate	4159	34.3	257	6.2
Demanding	4965	41.0	407	8.2
Strenuous	638	5.3	66	10.3
Influence at work				
High	4776	39.5	322	6.7
A certain	6051	50.0	457	7.5
Very low	1072	8.9	70	6.5
No	194	1.6	20	10.3
Predisposition IHD				
No	10,091	83.4	670	6.6
Yes	691	5.7	83	12.0
Unknown	1233	10.2	111	9.0
Missing	78	0.7	5	6.4
Diabetes				
No	11,925	98.6	844	7.1
Yes	103	0.9	21	20.4
Missing	65	0.5	4	6.1
BMI				
≤18.5	294	2.4	26	8.8
>18.5 to <25	8529	70.5	532	6.2
≥25 to <30	2626	21.7	234	8.9
≥30	605	5.0	75	12.4
Missing	39	0.4	0	0
Smoking				
Never	4058	33.6	244	6.0
Former	3062	25.3	202	6.6
Current	4472	37.0	393	8.8
Missing	501	4.1	30	6.0
Alcohol intake				
No alcohol intake	1658	14.5	144	8.7
<15 U/Wk	7336	63.8	498	6.8
15–21 U/Wk	1484	12.6	97	6.5
>21 U/Wk	1176	9.1	93	7.9
Missing	439	3.6	37	8.4
Leisure time physical activity				
Vigorous	3290	27.2	225	6.8
Moderate	8069	66.7	582	7.2
Sedentary	649	5.4	57	8.8
Missing	85	0.7	5	5.9
Work pressure				
Suitable	4639	38.4	295	6.4
A little too high	5673	46.9	438	7.7
Much too high	1664	13.8	128	7.7
A little/much too low	117	1.0	8	6.8
Shift work				
Day	7406	61.3	512	6.9
Evening	1502	12.4	117	7.8
Night	937	7.7	95	10.1
Rotate	2238	18.5	145	6.5
Missing	10	0.1	0	0
Working hours per week				
1–29 h	3540	29.4	260	7.3
30–40 h	8077	67.1	581	7.2
>40 h	416	3.5	24	5.8
Missing	60	0.4	2	3.3

869 cases of IHD during follow-up 1993–2013

IHD ischaemic heart disease, *n* number of subjects, *U* unit of alcohol, *Wk* week

[a]These percentages are the number of nurses in the category/12,093 × 100

[b]These percentages are the number of cases of IHD in the category/number of nurses in the category × 100

and the number and frequency of cases of IHD in the categories of all variables.

Associations between OPA and influence at work and risk of IHD

In Table 2, the association between all four categories of OPA and influence at work, respectively, and the risk of IHD is shown.

Nurses with demanding OPA had 22% higher risk of developing IHD and nurses with strenuous OPA had 41% higher risk of developing IHD compared to those with moderate OPA in the fully adjusted model. The risk of IHD among nurses with sedentary OPA was not different from those with moderate OPA. Nurses with some or very low influence at work did not have significantly different risk of IHD compared to those with high influence at work. Nurses with no influence at work tended to have a higher risk of IHD, but the group comprised of 194 nurses and the estimate was not statistically significant (Table 2).

Table 2 The effect of including potential confounders/mediating factors on hazard ratio (HR) for ischaemic heart disease (IHD) according to physical activity at work and influence at work among 12,093 female nurses participating in the Danish Nurse Cohort Study 1993–2013

	n	Basic model 1[a]		Adjusted model 2[b]	
		HR	95% CI	HR	95% CI
Physical activity at work					
Sedentary	2331	1.04	0.84–1,28	1.01	0.81–1.27
Moderate	4159	1	–	1	–
Demanding	4965	1.27	1.08–1.48	1.22	1.03–1.44
Strenuous	638	1.66	1.27–2.18	1.41	1.04–1.92
Influence at work					
High	4776	1	–	1	–
Some	6051	1.04	0.90–1.20	0.99	0.84–1.15
Very low	1072	0.92	0.71–1.19	0.89	0.67–1.18
No	194	1.50	0.96–2.35	1.31	0.80–2.13

869 cases of IHD during follow-up

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *IHD* ischaemic heart disease, *OPA* physical activity at work, *n* number of subjects

[a]Basic model 1: adjusted for age

[b]Adjusted model 2: adjusted for age and risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), leisure time physical activity, work pressure, work hours and shift work and mutually adjusted for OPA and influence at work

Multiplicative interaction, combined exposure to OPA and influence at work and risk of IHD

Table 3 presents the association of the combined exposure to OPA and influence at work, and the risk of IHD with a common reference group: moderate OPA and high influence at work. Furthermore, Table 3 shows the association between OPA and risk of IHD within strata of influence at work. These results are from the same model and therefore, some of the estimates are identical.

The fully adjusted model with a common reference group showed that nurses with strenuous OPA and low influence at work had a statistically significant 46% higher risk of IHD than nurses with moderate OPA and high influence at work. Nurses with strenuous OPA and high influence at work, however, did not have an increased risk of IHD neither in the age-adjusted nor in the fully adjusted model. The risk of IHD among nurses with demanding OPA did not differ according to level of influence at work in comparison to nurses with moderate OPA and high influence at work.

The fully adjusted model of the stratified analysis (Table 3) showed that among nurses with low influence at work, those with strenuous OPA had 71% higher risk of IHD compared to those with moderate OPA, but that among nurses with high influence at work, those with strenuous OPA did not have a significantly higher risk of

Table 3 Hazard ratio (HR) and 95% CI for ischaemic heart disease (IHD) according to interplay between physical activity at work (OPA) and influence at work (the results with a common reference group and the effects of OPA within strata of influence at work are from the same Cox PH model including an interaction term between OPA and influence at work, and therefore, some of the estimates are identical)

Combination of OPA and influence at work	No. of subjects/ no. with IHD	Common reference group for OPA and influence at work				Effect of OPA within strata of influence at work			
		Basic model 1[a]		Adjusted model 2[b]		Basic model 1[a]		Adjusted model 2[b]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
High influence at work sedentary OPA	1481/81	0.87	0.65–1.16	0.87	0.64–1.17	0.87	0.65–1.16	0.87	0.64–1.17
High influence at work moderate OPA	1598/106	1		1		1		1	
High influence at work demanding OPA	1544/124	1.18	0.91–1.53	1.13	0.86–1.49	1.18	0.91–1.53	1.13	0.86–1.49
High influence at work strenuous OPA	153/11	1.07	0.57–1.99	1.10	0.59–2.06	1.07	0.57–1.99	1.10	0.59–2.06
Low influence at work sedentary OPA	850/58	1.06	0.77–1.47	1.06	0.77–1.48	1.25	0.93–1.70	1.24	0.91–1.70
Low influence at work moderate OPA	2561/151	0.85	0.66–1.09	0.85	0.66–1.11	1		1	
Low influence at work demanding OPA	3421/283	1.13	0.91–1.42	1.14	0.90–1.46	1.33	1.09–1.63	1.34	1.08–1.66
Low influence at work strenuous OPA	485/55	1.64	1.18–2.27	1.46	1.02–2.09	1.93	1.42–2.62	1.71	1.22–2.40

12,093 female nurses from the Danish Nurse Cohort Study. 869 cases of IHD during follow-up 1993–2013

Measure of effect modification on multiplicative scale: OPA x influence at work: $p = 0.184$ (Basic model 1)

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *IHD* ischaemic heart disease, *OPA* physical activity at work

[a]Model 1: age as underlying time scale

[b]Model 2: adjusted for age and risk factors for IHD (family history of IHD, diabetes, BMI, smoking and alcohol consumption), leisure time physical activity, work hours and shift work

IHD than those with moderate OPA. Demanding OPA was associated with 34% higher risk of IHD compared to moderate OPA among nurses with low influence at work. Among nurses with high influence at work, the risk of IHD from demanding OPA was not significantly different from the risk from moderate OPA. The *p* value for the multiplicative interaction term between OPA and influence at work was $p=0.184$ (Table 3).

Additive hazards model

Table 4 presents the result of an additive hazards model and shows the number of additional cases of IHD per 10,000 person years associated with different combinations of OPA and influence at work and the result of a test for additive interaction.

Compared to nurses with moderate OPA and high influence at work, those with strenuous OPA and low influence at work had 18.0 additional cases of IHD per 10,000 person years in the fully adjusted model. Among nurses with strenuous OPA and high influence at work the number of additional cases of IHD was not significantly different compared to the reference group. Nurses with demanding OPA and low influence at work did not have a statistically significant different number of additional cases of IHD compared to the reference group and this was similar among those with demanding OPA and high influence at work. There was a marginally significant additive interaction between strenuous OPA and influence at work in the age-adjusted analysis ($p=0.065$) that could explain the additional cases among those with strenuous OPA and low influence at work.

Sensitivity analyses

In a sensitivity analysis, the model 2 found in Tables 3 and 4 was further adjusted for work pressure (Tables 3, 4). This slightly attenuated the associations in the two models, but did not change their directions (data not shown). We further investigated possible three-way interaction between work pressure, OPA and influence at work, but did not find a significant interaction ($p=0.974$).

The age-adjusted association between risk of IHD and OPA and influence at work, respectively, was investigated

Table 4 Additive hazards model. Estimation of absolute size of the additional numbers of cases of incident ischaemic heart disease (IHD) and 95% confidence interval (CI) due to the combined effect of physical activity at work (OPA) and influence at work for 12,093 female nurses from the Danish Nurse Cohort Study, 1993–2013

	No. of subjects/ no. with IHD	Basic model 1[a]		Adjusted model 2[b]	
		Additional cases of IHD/10,000 person years	95% CI (*p* value)	Additional cases/10,000 person years	95% CI (*p* value)
High influence at work Sedentary OPA	1481/81	−4.2	−13.4 to 5.0 (0.372)	−4.6	−14.7 to 5.6 (0.377)
High influence at work Moderate OPA	1598/186	1		1	
High influence at work Demanding OPA	1544/124	6.5	−3.3 to 16.3 (0.194)	4.6	−6.2 to 15.5 (0.404)
High influence at work Strenuous OPA	153/11	2.4	−21.6 to 26.3 (0.847)	4.0	−23.5 to 31.6 (0.774)
Low influence at work Sedentary OPA	859/58	2.3	−9.2 to 13.7 (0.702)	2.2	−9.9 to 14.4 (0.722)
Low influence at work Moderate OPA	2561/151	−5.5	−13.8 to 2.8 (0.197)	−4.9	−13.6 to 3.9 (0.277)
Low influence at work Demanding OPA	3421/283	5.0	−3.2 to 13.1 (0.233)	5.2	−4.1 to 14.5 (0.269)
Low influence at work Strenuous OPA	485/55	23.7	6.6 to 40.7 (0.006)	18.0	−0.01 to 36.0 (0.050)

Measure of additive interaction between demanding OPA and influence at work: 3.9 (−8.3 to 16.2) additional cases of IHD/10,000 person years, $p=0.531$ (basic model 1)

Measure of additive interaction between strenuous OPA and influence at work: 26.8 (−1.6 to 55.3) additional cases of IHD/10,000 person years, $p=0.065$ (basic model 1)

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *IHD* ischaemic heart disease, OPA physical activity at work

[a]Basic model 1 age as underlying time scale

[b]Adjusted model 2 age as underlying time scale. Additionally adjusted for traditional risk factors for IHD: (family history of IHD, diabetes, BMI, smoking and alcohol consumption), physical activity during leisure time, work hours per week and shift work

in an additional sensitivity analysis where the nurses were censored when they became 70 years. This revealed a stronger association between strenuous [HR 1.79 (95% CI 1.29–2.47)] and demanding [HR 1.42 (95% CI 1.18–1.71)] OPA and risk of IHD than in the main analysis. Furthermore, in this analysis having no influence at work was associated with a significantly higher risk of IHD [HR 1.81 (95% CI 1.09–3.00)].

Discussion

The aim of this study was to investigate whether influence on the organisation of the daily work had a modifying effect on the association between demanding and strenuous OPA and risk of IHD and thus whether having high influence at work could reduce the adverse effect of strenuous or demanding OPA on the risk of IHD. The results showed that compared to nurses with moderate OPA and high influence at work, those with strenuous OPA and low influence at work had 46% higher risk of IHD, whereas nurses with high influence at work did not have an increased risk of IHD from strenuous OPA. An analysis of the association between OPA and IHD in strata of influence at work also indicated an increased risk of IHD from strenuous OPA among those with low influence at work, but not among those with high influence at work. There was no indication of a different risk of IHD from demanding OPA dependent on the level of influence at work in the analysis with a common reference group. We did not find statistically significant multiplicative interaction between OPA and influence at work. However, the results from the multiplicative model did indicate heterogeneity in the risk of IHD from strenuous work dependent on the level of influence at work. Therefore, we used an additive hazards model to investigate whether this was due to an adverse additive interaction effect of combined exposure to strenuous OPA and low influence at work. The additive model showed that compared to nurses with moderate OPA and high influence at work, those with strenuous OPA and low influence at work had 18 additional cases of IHD per 10,000 person years, whereas those with strenuous OPA and high influence at work did not have a statistically significantly higher number of cases of IHD compared to the reference group. The *p* value for the additive interaction between strenuous OPA and influence at work was 0.065 and thus marginally statistically significant. This additive interaction explained the additional cases among nurses with strenuous OPA and low influence at work compared to those with moderate OPA and high influence at work.

Among those with demanding OPA, the level of influence at work did not seem to influence the association between demanding OPA and risk of IHD.

Though models exist concerning interaction of physical and psychosocial work environment and health (Stavroula and Aditya 2010) and this question has been examined with other health outcomes, e.g. musculoskeletal disorders (Devereux et al. 2002), we have only been able to identify three previous studies focusing on a joint effect of psychosocial work factors and OPA on the risk of IHD. One study from 1988 among male and female metal workers investigated the association between a combined measure of physical strain at work, variety at work and job control—called job strain—and risk of IHD. The study showed that this measure of job strain was associated with increased risk of IHD (Haan 1988). Another study from 1985 among male workers showed that the standardised hospitalisation ratio for MI was higher from the combination of hectic work and heavy lifting than from heavy lifting alone (Alfredsson et al. 1985). In a recent study from Belgium, the potential buffering effect of job control and social support at work on the association between physical work demands and IHD was investigated. In that study, a buffering effect of social support on the association between high OPA and IHD was shown. There was, however, no indication of a similar buffering effect of job control (Clays et al. 2016). Different measures of job control could be one explanation for the different findings in the present study and in the study from Belgium. In the study from Belgium, job control was measured by the Job Content Questionnaire by Karasek et al. (Clays et al. 2016; Karasek et al. 1998), which covers both skill discretion and decision authority. The single question in the present study only concerned one of the different aspects of job control covered in the Job Content Questionnaire. It could be that decision authority, e.g. the ability to plan and organise one's work tasks is more important in counteracting a detrimental effect of physically strenuous work on heart health than the level of skill and creativity that is required on the job. A sensitivity analysis in the study from Belgium did, however, not find any modifying effect of either of the two separate sub-dimensions of job control.

Overall, all analyses presented in the present study indicated a modifying effect of influence at work on the association between strenuous OPA and risk of IHD. There was a difference in the risk of IHD and number of additional cases of IHD in the group of nurses with strenuous OPA dependent on the level of influence at work. Furthermore, the additive model indicated that the additional cases of IHD among nurses with strenuous OPA and low influence at work were due to a detrimental interaction between the two exposures. This suggests that nurses with the combination of strenuous OPA and low influence at work may be at particular risk of IHD, and that there could be a potential for prevention of IHD among workers with strenuous OPA and low influence at work by altering either or both of these exposures. In this study, having low influence at work was not independently associated with an increased risk of IHD, but the results indicated that changing the level of influence at work from low to high may be a possible approach to prevent IHD among those with strenuous work. High influence at work, especially the aspects that concerns authority to plan and organise work tasks, could improve the nurses' possibilities to influence their working situation, to better adjust their physical demands to their own capacity, to distribute strenuous tasks over the work day and to ensure that periods of physically demanding work tasks are interspersed with pauses and rest.

We encourage future studies to include job groups who to a larger extent are exposed to physically strenuous work and low influence at work to elucidate whether high influence at work can buffer and prevent some of the cases of IHD among those exposed to strenuous work.

In our previous study with 15 years follow-up in this cohort, we showed that high OPA increased the risk of IHD (Allesoe et al. 2015). However, we did not have enough cases in the group of nurses with strenuous work to distinguish between demanding and strenuous work (Allesoe et al. 2015). In the present study, we had more cases of IHD due to 5 more years of follow up. As a secondary finding, the results indicate a dose response association between OPA and IHD from moderate through demanding OPA to strenuous OPA. The risk of IHD among nurses with sedentary work did not differ from those with moderate OPA.

Strengths and limitations

A major strength of this study is the large cohort of women, the relatively high number of cases of IHD due to 20 years of follow-up and the prospective design. The study was based on the entire population of Danish nurses with a very high response rate. A further strength of the study was that the information on incident and previous IHD was obtained through individual linkage to a nationwide hospital register that has almost complete coverage. In addition, the follow-up period for the nurses was nearly complete. However, some less harmful cases of angina pectoris may have been treated in general practice and thus not registered in the Danish National Patient Registry. This might have caused a small degree of non-differential misclassification, which could lead to underestimation of effects. A sensitivity analysis with myocardial infarction and other types of IHD apart from angina pectoris as outcome in a previous study, however, showed an even stronger association between demanding and strenuous OPA and risk of IHD (Allesoe et al. 2015). That finding indicated that bias from including symptom-based angina pectoris did not explain the findings.

Studies have shown that both job control (Marmot and Davey 1997; Marmot et al. 1997) and OPA (Beenackers et al. 2012; Holtermann et al. 2012a) were associated with socioeconomic status. In the present study, all nurses had the same profession and education, which reduced the risk of socioeconomic confounding. A study based on one profession only could, however, lead to less heterogeneity in the distribution of the occupational exposures. With regard to OPA, Danish nurses have a range of different physical demands at work and this was reflected in the distribution between the four OPA categories in the present study. There was, however, less contrast in exposure regarding influence at work. The majority of nurses had high or a certain influence at work and this led to a small number in combinations of OPA with very low or no influence at work. Consequently, and to reduce the number of categories, we dichotomised influence at work into high versus low in these analyses, and we were thus not able to explore the combined effect on the risk of IHD of OPA and all the levels of influence at work.

The assessment of OPA and influence at work was based on single questions and were rather crude. However, the HR's that were observed in the present study were in line with HR's obtained in former studies, some of them using more extensive assessments of OPA and influence at work (Li et al. 2013; Theorell et al. 2016).

All exposure variables were measured at one time point. Given, we had around 20 years of follow-up, the youngest nurses were 45 years old at the start of the study and that the average retirement age in Denmark was 65 years, the majority of the nurses were retired at the end of follow-up. This could have resulted in some degree of nondifferential misclassification, which may have diluted the associations, because the nurses no longer were experiencing work exposures. To reduce the time at risk for those no longer exposed to work factors, we performed a sensitivity analysis where nurses were censored when they became 70 years old. That analysis showed a stronger association between strenuous and demanding OPA, respectively, and risk of IHD than in the main analysis, which indicates that these associations could be somewhat diluted due to an increasing number of nurses retired and with no occupational exposure during follow-up.

We adjusted for the occupational risk factors of shift work and work hours in all fully adjusted models in this study, and in a sensitivity analysis, we further included work pressure. The reason for including work pressure only in the sensitivity analysis was that especially influence at work, but also OPA were associated with work pressure in this study (data not shown). Consequently, adjustment for work pressure could make it difficult to separate the effects of OPA and influence at work from the effect of work pressure. However, adjustment for work pressure only slightly attenuated the estimates and we did not find three-way interaction among work pressure, OPA and influence at work.

Conclusion

In this cohort of nurses, a modifying effect of influence at work on the risk of IHD from strenuous OPA was observed. Strenuous OPA in combination with low influence at work was associated with a higher risk of IHD, which was not found in combination with high influence at work. A detrimental additive interaction between strenuous OPA and low influence at work was indicated, which implies that this group may be at a particular risk of IHD. This also suggests a potential for IHD prevention by altering low influence at work to high among those with strenuous OPA.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

References

Alfredsson L, Spetz CL, Theorell T (1985) Type of occupation and near-future hospitalization for myocardial infarction and some other diagnoses. Int J Epidemiol 14(3):378–388

Allesoe K, Holtermann A, Aadahl M, Thomsen JF, Hundrup YA, Sogaard K (2015) High occupational physical activity and risk of ischaemic heart disease in women: the interplay with physical activity during leisure time. Eur J Prev Cardiol 22(12):1601–1608

Beenackers MA, Kamphuis CB, Giskes K, Brug J, Kunst AE, Burdorf A, van Lenthe FJ (2012) Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: a systematic review. Int J Behav Nutr Phys Act 9:116

Clays E, Casini A, Van HK, De BD, Kittel F, De Bacquer G, Holtermann A (2016) Do psychosocial job resources buffer the relation between physical work demands and coronary heart disease? A prospective study among men. Int Arch Occup Environ Health. doi:10.1007/s00420-016-1165-z

Det Nationale Forskningscenter for Arbejdsmiljø (2010) Arbejdsmiljøprofil for sygeplejersker. http://www.arbejdsmiljoforskning.dk/da/arbejdsmiljoedata/flere-datasaet/arbejdsmiljo-og-helbred/alle-svar-for-jobgrupper/diagram?group=NAK10_Jobgrp_1104. Accessed 14 Jan 2017

Devereux JJ, Vlachonikolis IG, Buckle PW (2002) Epidemiological study to investigate potential interaction between physical and psychosocial factors at work that may increase the risk of symptoms of musculoskeletal disorder of the neck and upper limb. Occup Environ Med 59(4):269–277

Eurofound (2015) First findings: sixth European working conditions survey. Publications Office of the European Union, Luxembourg

Haan MN (1988) Job strain and ischaemic heart disease: an epidemiologic study of metal workers. Ann Clin Res 20(1–2):143–145

Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A (1998) Is the effect of job strain on myocardial infarction risk due to interaction between high psychological demands and low decision latitude? Results from Stockholm Heart Epidemiology Program (SHEEP). Soc Sci Med 46(11):1405–1415

Harari G, Green MS, Zelber-Sagi S (2015) Combined association of occupational and leisure-time physical activity with all-cause and coronary heart disease mortality among a cohort of men followed-up for 22 years. Occup Environ Med 72(9):617–624

Häusser JA, Mojzisch A, Niesel M, Schulz-Hardt S (2010) Ten years on: a review of recent research on the Job Demand-Control (-Support) model and psychological well-being. Work Stress 24(1):1–35

Holtermann A (2015) Occupational and leisure-time physical activity and coronary heart disease. Occup Environ Med 72(9):615–616

Holtermann A, Burr H, Hansen JV, Krause N, Sogaard K, Mortensen OS (2012a) Occupational physical activity and mortality among Danish workers. Int Arch Occup Environ Health 85(3):305–310

Holtermann A, Marott JL, Gyntelberg F, Sogaard K, Suadicani P, Mortensen OS, Prescott E, Schnohr P (2012b) Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. BMJ Open 2(1):e000556

Hu GC, Chien KL, Hsieh SF, Chen CY, Tsai WH, Su TC (2014) Occupational versus leisure-time physical activity in reducing cardiovascular risks and mortality among ethnic Chinese adults in Taiwan. Asia Pac J Public Health 26(6):604–613

Hundrup YA, Simonsen MK, Jorgensen T, Obel EB (2012) Cohort profile: the Danish nurse cohort. Int J Epidemiol 41(5):1241–1247

Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B (1998) The job content questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. J Occup Health Psychol 3(4):322–355

Karasek R, Theorell T (1990) Healthy work. Stress, productivity and the reconstruction of working life. Basic Books, New York

Karlqvist LK, Harenstam A, Leijon O, Scheele P (2003) Excessive physical demands in modern worklife and characteristics of work and living conditions of persons at risk. Scand J Work Environ Health 29(5):363–377

Kasl SV (1996) The influence of the work environment on cardiovascular health: a historical, conceptual, and methodological perspective. J Occup Health Psychol 1(1):42–56

Kivimaki M, Kawachi I (2015) Work stress as a risk factor for cardiovascular disease. Curr Cardiol Rep 17(9):630

Kivimaki M, Nyberg ST, Batty GD et al (2012) Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet 380(9852):1491–1497

Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 145(1):72–80

Li J, Loerbroks A, Angerer P (2013) Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? Curr Opin Cardiol 28(5):575–583

Marmot M, Davey SG (1997) Socio-economic differentials in health. J Health Psychol 2(3):283–296

Marmot MG, Bosma H, Hemingway H, Brunner E, Stansfeld S (1997) Contribution of job control and other risk factors to

social variations in coronary heart disease incidence. Lancet 350(9073):235–239
Mosca L, Barrett-Connor E, Wenger NK (2011) Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 124(19):2145–2154
Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M (2012) European cardiovascular disease statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis
Petersen CB, Eriksen L, Tolstrup JS, Sogaard K, Gronbaek M, Holtermann A (2012) Occupational heavy lifting and risk of ischemic heart disease and all-cause mortality. BMC Public Health 12:1070
Richard A, Martin B, Wanner M, Eichholzer M, Rohrmann S (2015) Effects of leisure-time and occupational physical activity on total mortality risk in NHANES III according to sex, ethnicity, central obesity, and age. J Phys Act Health 12(2):184–192
Rod NH, Lange T, Andersen I, Marott JL, Diderichsen F (2012) Additive interaction in survival analysis: use of the additive hazards model. Epidemiology 23(5):733–737
Saltin B, Grimby G (1968) Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 38(6):1104–1115
Sørensen L (2017) Sygeplejerskers fysiske arbejdsmiljø 2012 med fokus på muskelskelet belastninger. Dansk Sygeplejeråd. https://dsr.dk/sites/default/files/24/notat_fysisk_arbejdsmiljoe_blandt_sygeplejersker_2012_0.pdf. Accessed 14 Jan 2017
Stavroula L, Aditya J (2010) Health impact of psychosocial hazards at work: an overview. WHO, Geneva
Theorell T, Jood K, Jarvholm LS, Vingard E, Perk J, Ostergren PO, Hall C (2016) A systematic review of studies in the contributions of the work environment to ischaemic heart disease development. Eur J Public Health 26(3):470–477
VanderWeele TJ, Knol MJ (2014) A tutorial on interaction. Epidemiol Methods 3(1):33–72
Wethje A, Borg W (2006) Sygeplejerskers arbejdsmiljø, trivsel of helbred (SATH). Dansk Sygeplejeråd og Arbejdsmiljøinstituttet, København