Prospective relationship between occupational physical activity and risk of ischemic heart disease - are men and women differently affected?

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Abstract:

Background: High occupational physical activity (OPA) seems to increase risk of CVD among men. However, findings are mixed, and it is not known if women are differently affected.

Aims: To investigate the relationship between OPA and risk for ischemic heart disease (IHD), and whether it differs across sex.

Methods: A prospective cohort study based on 1,399 women and 1,706 men, aged 30–61 years, participating in the Danish Monica 1 study in 1982–84, actively employed, without prior IHD and answering an OPA question. Information on incidence of IHD, before and during the 34-years follow-up, was retrieved by individual linkage to the Danish National Patient Registry. Cox proportional hazards models were used to investigate the association between OPA and IHD.

Results: Compared to women with sedentary work, women in all other OPA categories had lower hazard ratio (HR) for IHD. Among men, the risk of IHD was 22% higher among those with light OPA, and 42% and 46% higher among those with moderate OPA with some lifting or strenuous work with heavy lifting, respectively, compared to men with sedentary OPA. Compared to women with sedentary work, HR for IHD was higher among men in all OPA categories. There was statistically significant interaction between OPA and sex.

Conclusion: Demanding or strenuous OPA seems to be a risk factor for IHD among men, whereas a higher level of OPA seems to protect from IHD among women. This emphasizes the importance of taking sex-differences into account in studies of health effects of OPA.

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Lay summary.

In the Danish Monica I study among 1,399 women and 1,706 men we investigated whether high physical activity at work was associated with higher risk of ischemic heart disease and whether this association was different among men and women.

The association between occupational physical activity and ischemic heart disease was different among men and women

High physical activity at work was associated with around 45% higher risk of ischemic heart disease in men, but with around 65% lower risk in women

The underlying mechanisms for this difference e.g., differences in exposure and physiology should be further investigated in future studies

Keywords

Physical activity

Work

Heart diseases

Sex differences

Epidemiology

Introduction

Globally and in European countries, cardiovascular diseases (CVD) are among the leading causes of mortality (1, 2). Furthermore, in 2017 in Europe, there were 108.7 million people living with CVD, hereof 34.9 million living with ischemic heart disease (IHD) (1).

Leisure time physical activity (LTPA) is well-known to promote health and to prevent many chronic diseases including CVD (3). However, the beneficial cardiovascular effect of physical activity may depend on the domain i.e. whether physical activity is performed at work or during leisure time, and on the characteristics of performed activities (4). A recent review showed that whereas leisure time physical activity (LTPA) was protective, high occupational physical activity (OPA) did not protect from CVD mortality (5), and a recent study in a large population showed lower risk of major adverse cardiovascular events from LTPA but higher risk from high OPA (6). It is suggested that fundamental differences between LTPA and OPA including differences in intensity, amount of static versus dynamic movements, duration, and time for recovery may be possible explanations of these seemingly opposing associations with health, the so-called the physical activity health paradox (7).

In studies analyzing men and women separately, some studies among men showed detrimental effects of high OPA on cardiovascular health (8-12). Yet other studies did not find an association between OPA and heart disease, specifically, or CVD, including conditions affecting the heart and blood vessels, in men (13, 14). Among women, a few studies showed (15) or indicated (9, 16) that high OPA was associated with increased risk of heart disease, whereas other studies have indicated a protective effect or shown no association (8, 11, 12, 17). However, beneficial effects of OPA with respect to risk of heart disease and CVD have also been observed among both women (18, 19) and men (17-19), so overall the findings are mixed. Some studies have included both men and women and have analysed men and women separately, but very few have tested whether there is a sex difference (6, 9, 20). Both in a previous paper on gender and occupational health (21), and in a recent paper on the future agenda for studies of the association between health and LTPA and OPA, respectively (22), one of the recommendations was to further explore differences between men and women. Women have an average 7-to-10- year delay in the first manifestation of heart diseases compared to men (23) and there are sex-differences in basal metabolism, hormones, physical capacity and muscle strength, that may play a role in both the physical impact and perception of a given workload (24, 25). Furthermore, there is extensive gender segregation in the labor market, especially in jobs with high physical demands (26) and even though men and women have the same occupational titles, there are large differences in their physical working conditions (27).

The aim of the present study was to investigate the relationship between OPA and risk for IHD and possible differences in this relationship between men and women in the Danish Monica I (Monitoring Trends and Determinants of Cardiovascular Disease) Study. Our hypothesis is that demanding or strenuous OPA is associated with a higher risk of IHD than lower levels of OPA, irrespective of sex.

Methods

Study population and exclusion criteria

The Danish Monica I study was conducted from 1982 to 1984. From the Danish Central Person Register 4,807 persons, hereof 2,404 men and 2,403 women from 11 municipalities in the western part of Copenhagen Region, born in 1922, 1932, 1942 or 1952, were drawn as a random selection and were invited to participate in the Danish Monica I health survey. Totally 4,807 were invited, hereof 968 individuals aged 30, 980 aged 40, 965 aged 50, and 872 aged 60. The participation rate was 79%. After exclusion of those not actively employed at baseline, with missing information on OPA or with a hospital admission with IHD before baseline, the study population consisted of 3,105 respondents, hereof 1,706 men and 1,399 women (figure 1).

Figure 1. Flowchart of participants in the Monica Study and formation of the study population.

[Figure 1]

Study design

A prospective cohort study based on data from the Danish Monica 1 study with baseline at the date of health examination of each participant in 1982–84 and with register-based information on incident IHD during follow-up until December 20, 2016.

Endpoints

Information about incident cases of IHD was retrieved by individual linkage of a personal identification number assigned to all residents in Denmark to the Danish National Patient Registry (28) in the period from this registry was initiated in 1977 and until end of follow-up. IHD was classified according to the WHO International Classification of Diseases (ICD 10 (from 1994) and ICD 8 (from 1977 until the end of 1993) and IHD cases were defined as hospitalisation for myocardial infarction (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).

Participants were censored as cases at their first event (first ever hospitalisation with IHD). Otherwise, they were censored when they died at or out of hospital, when they were classified as emigrated and could no longer be followed in the registers, and otherwise at the end of the follow-up. Information on date of death or classification as emigrated was retrieved from the Central Person Registry.

Assessment of occupational physical activity

OPA was assessed by a single question, based on the Saltin and Grimby question (29). Classification is shown in parenthesis:

To which of the following groups do you belong at your workplace - outside or at home:

a. Mainly sedentary: desk work, assemble small parts and the like (sedentary)
b. Work involving some walking but no carrying heavy items: light industrial work, non-sedentary office work, inspection, kitchen work, housework, teaching and the like (light)
c. Mainly walking, work involving climbing stairs and some lifting: mail delivery, construction work, move heavy furniture and the like (moderate, some lifting)
d. Physically demanding work with heavy lifting: excavation work, forestry, concrete work, and the like (strenuous, heavy lifting)

Assessment of covariates

Register based covariates: Sex (considered both a biological and a cultural/psychosocial factor) and age at the time of the health examination was retrieved from the Central Person Registry. Participants were included in the study according to four specific years of birth (30, 40, 50 and 60 years old at invitation to participate) but due to two years of inclusion time, the categorical age-variable formed was: 30-32, 40–42, 50–52, 60-62.

Covariates assessed at baseline investigations: At a health examination clinical and biochemical data were collected, participants were interviewed, and a self-report questionnaire was filled out. For the assessment of medication use, the participants were asked to bring their medication used currently or during the last 12 months before baseline. The wording of the questions, measurement methods and categorization of the covariates is found in section A in appendix.

Sociodemographic and socioeconomic factors (SES): cohabitation status and vocational education.

Additional known risk factors for IHD: LTPA, self-reported fitness, smoking, alcohol intake per week, family history of heart disease, diabetes, body mass index (BMI), blood lipids: high density lipoprotein (HDL), serum cholesterol, and triglyceride.

Occupational factors: work hours per week.

Variables for sensitivity analyses: blood pressure, hypertension.

Statistical methods

In a current paper on perspectives for future research in physical activity health paradox it is recommended to investigate sex-differences (22), hence it was decided a priori to do so, and to test for interaction between OPA and sex. This was done by inclusion of an interaction product term for OPA and sex (OPA*sex) and thereby allowing for the associations of OPA with the outcome to differ between sexes.

Population characteristics are presented by frequencies and percentages or mean and standard deviations (whenever appropriate) for the total population and for men and women and according to level of OPA.

Due to the competing risks of IHD and death, risks of both are presented by cumulative incidence (CI) curves for men and women. The Cumulative incidence curves are compared by Gray's test for equality (30).

Cox proportional hazards (Cox PH) models were used to test for associations between OPA and IHD. In the models, follow-up time was the underlying time scale. In all Cox PH models, 95% confidence intervals (CI) were calculated. From available covariates, potential confounders for the association between OPA and IHD were selected a priori based on current knowledge from the literature about their association with CVD (31, 32).

In the models without an interaction term, between OPA and sex, we analysed Model A: Adjusted for age and Model B: Adjusted for age and sex.

In a second model the association between OPA and IHD was allowed to differ according to sex by including a term of interaction. The result from this model is presented both with a common reference group (women with sedentary OPA) and as the effect of OPA on risk of IHD within sex-strata. The following models were analysed: Model 1: adjusted for age. Model 2: adjusted for age and LTPA. Model 3: model 2 additionally adjusted for smoking, alcohol, BMI, self-reported fitness, diabetes, serum cholesterol, HDL, triglycerides, familial predisposition for heart disease, working hours and civil status. Model 4: model 3 further adjusted for socioeconomic status (vocational education).

Furthermore, the interaction between OPA and age, and OPA and LTPA was assessed.

The adequacy of the cox proportional regression model was assessed by cumulative sums of martingale-based residuals (33).

As OPA is associated to socioeconomic status (SES) (12, 34), we made a sensitivity analysis of the age-adjusted association between OPA and IHD among those with the lowest level of vocational training: without or ≤ 1 years of training.

An increased systolic blood pressure (SBP) or hypertension may be in the causal pathway from high OPA to IHD and therefore we performed a separate sensitivity analysis where model 1 and 4 was further adjusted for SBP and made an analysis where model 1 was stratified by hypertension.

Finally, as the follow-up time in the present study is long and participants may have changed exposure to OPA, e.g., due to retirement, the age-adjusted association between OPA and IHD was investigated in a model with 20 years follow-up time.

In all analyses, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the statistical package SAS version 9.4.

Results

The study population included 3,105 respondents, 1,706 men and 1,399 women. Average follow-up time was 25.5 years (0.2–34.2 years) for men and 29 years (0.5–34.2 years) for women. The total number of person-years was 43,502.4 years for men and 40,529.3 years for women. During follow-up 358 men and 152 women were admitted to hospital with IHD. Of the remaining 1,348 men and 1,247 women, 594 men and 394 women died during follow-up, 20 men and 12 women emigrated or could otherwise no longer be followed in the registers. There were 734 men and 841 women, who were followed until the end of follow-up.

Table 1 presents the baseline characteristics of the study population among men and women. The mean age was 44.2 years among men and 42.8 years among women.

Table 1. Characteristics (number and percentages or mean and standard deviation (SD)) among 1,706 men and 1,399 women participating in the Danish Monica 1 Study.

[Table 1]

*Due to anonymization, n is not shown, where the number of missing observations was under 5. #SBP≥140 or DBP≥90 or using antihypertensive medication or self-report of hypertension. OPA: occupational physical activity; LTPA: physical activity during leisure time; BMI: body mass index; AMI: acute myocardial infarct. HDL: High density lipoprotein.

Figure 2a and b shows the CI-curves among women and men.

Figure 2a and b. The cumulative incidence curves for hazard of both IHD at any given time during follow-up from baseline to end of follow-up among a. women and b. men.

[Figure 2]

Among women, those with sedentary OPA had the highest probability of experiencing IHD during most of the follow-up period. Women with light OPA had the lowest probability of IHD, except for strenuous OPA, where there were very few cases of IHD. Among men, those with strenuous OPA had the highest probability of IHD during most of the follow-up period. Men with sedentary OPA had the lowest probabilities of IHD during most of the follow-up period, especially in the last part of follow-up. There were no statistically significant differences according to Gray’s test.

In figure B in appendix is a figure of the cumulative incidence curve (CI-curve) of the probability of experiencing all-cause mortality - given no previous case of IHD - in each OPA category at any given time during follow-up. Among men, those with moderate OPA had the highest and those with strenuous OPA had the lowest probability of all-cause mortality during most of the follow-up period. Among women, the curve shows that those with moderate OPA had the lowest probability of all-cause mortality during most of follow-up (figure B in appendix).

Assessment of the adequacy of the cox proportional regression model showed that the model assumption of proportional hazards was in accordance with data.

Table 2 presents the association between OPA and IHD among all participants. The age-adjusted HR for IHD was higher, the higher the level of OPA, and was 1.49 (95% CI 1.00–2.22) for strenuous work compared to sedentary work in the age-adjusted analysis (table 2). Further adjusting for sex especially attenuated the estimate for strenuous OPA and adjustment for all covariates in model C further attenuated the estimates (table 2).

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to level of occupational physical activity (OPA) among 1,706 men and 1,399 women participating in the Danish Monica 1 Study, 1982–84. 358 cases among men and 152 among women of IHD during follow-up until December 2016.

[Table 2]

Model A: Adjusted for age. Model B: Adjusted for age and sex. Model C: Adjusted for age, sex, leisure time physical activity, family history of heart disease, diabetes, body mass index (BMI), serum cholesterol, high density lipoprotein (HDL), triglycerides, smoking, alcohol consumption, self-reported fitness, working hours, civil status and socioeconomic status (SES).

To investigate if the association between OPA and IHD differed by sex, an interaction-term between OPA and sex was included, showing a statistically significant interaction between OPA and sex (p=0.048 in model 1 and p=0.032 in model 4).

There was no statistically significant interaction between OPA and age (p=0.672), and OPA and LTPA (p=0.666).

All models below included an interaction term between OPA and sex. Table 3A shows HR for IHD from different levels of OPA in strata of men and women with sedentary work as reference category for both sexes.

Table 3A. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to level of occupational physical activity (OPA) and sex in a model with an interaction term between OPA and sex. 1,706 men and 1,399 women participating in the Danish Monica 1 Study, 1982–84. 358 cases among men and 152 among women of IHD during follow-up until December 2016.

[Table 3A]

Model 1: Adjusted for age. Model 2: Adjusted for age and leisure time physical activity. Model 3: Adjusted for age and leisure time physical activity, family history of heart disease, diabetes, body mass index (BMI), serum cholesterol, high density lipoprotein (HDL), triglycerides, smoking, alcohol consumption, self-reported fitness, working hours, civil status. Model 4: Model 3 including SES (socioeconomic status).
Data protection regulations in Denmark require a minimum of 5 individuals in each group. Therefore, we have collapsed number of cases in the moderate and strenuous categories among women. There were in total 21 cases of IHD in the moderate and strenuous categories among women.

Among women, HR for IHD was lower in all other OPA categories compared to sedentary work in the age adjusted analysis, showing a 20–40% lower risk of IHD among those with light or moderate work. The lowest HR was seen among women with strenuous work, this category, however, was small (Model 1). Among men the risk of IHD was 25% higher among those with light OPA, and 49% and 45% higher among those with moderate or strenuous work, respectively, compared to men with sedentary OPA in the age-adjusted analysis. Adjusting for LTPA had only minor impact on the estimates (Model 2). Further adjustment for several known risk factors for IHD, working time and civil status in model 3, resulted in a slight attenuation of the magnitude of the associations among both men and women. Further adjusting for SES in model 4 had only minor effects on the estimates (Table 3A).

Table 3B shows results from the same model but presented with a common reference group (women with sedentary OPA) to be able to see the combined effect of OPA and sex on risk of IHD. The estimates for women were the same as those in table 3A in model 1-4 as the reference group was the same. Among men, HR for IHD was higher in all OPA categories compared to women with sedentary OPA. In model 1 and 2 men with sedentary work had nearly 50% higher risk of IHD, men with light OPA had around 90% higher risk and men with moderate or strenuous OPA had more than two times higher risk of IHD compared to women with sedentary work (table 3B). However, further adjustment in model 3 especially attenuated the estimates among men. This was partly due to adjustment for

HDL and to a lesser degree due to adjustment for BMI. The adjustment in model 3 seemed to lower the sex-difference in risk of IHD among sedentary men and women and to a lesser extent the differences in risk of IHD between the other OPA categories among men and women, respectively. Further adjustment for SES in model 4 only led to minor changes in the estimates. Further adjustment for SES in model 4 only led to minor changes in the estimates. Table C in appendix shows the same model with sedentary men as reference group (Table C in appendix)

Table 3B. Hazard ratio (HR) and 95% confidence interval (CI) for ischaemic heart disease (IHD) according to level of occupational physical activity (OPA) with a common reference group: women with sedentary OPA in a model with an interaction term between OPA and gender. 1,706 men and 1,399 women participating in the Danish Monica 1 Study, 1982–84. 358 cases among men and 152 among women of IHD during follow-up until December 2016.

[Table 3B]

Model 1: Adjusted for age. Model 2: Adjusted for age and leisure time physical activity. Model 3: Adjusted for age and leisure time physical activity, family history of heart disease, diabetes, body mass index (BMI), serum cholesterol, high density lipoprotein (HDL), triglycerides, smoking, alcohol consumption, self-reported fitness, working hours, civil status. Model 4: Model 3 including socioeconomic status (SES). # Data protection regulations in Denmark require a minimum of 5 individuals in each group. Therefore, we have collapsed number of cases in the moderate and strenuous categories among women. There were in total 21 cases of ischemic heart disease (IHD) in the moderate and strenuous categories among women.

In a separate sensitivity analysis model 1 and 4 in table 3A was further adjusted for SBP. This only resulted in minor changes of the estimates (results not shown). We also stratified for hypertension in a sensitivity analysis to see whether individuals with hypertension had higher risk of IHD from high OPA than normotensive individuals (Table D in appendix). Among men, the largest difference between normotensives and hypertensives was among those with strenuous work, where HR for IHD compared to sedentary work was nearly twice as high among those with hypertension HR 1.97 (95% CI 0.99–3.92) but only 30% higher among normotensives HR 1.31 (95% CI 0.75–2.27). However, there were only 31 hypertensive men with strenuous work. Among women, a u-shaped association was indicated among hypertensive women with a lower risk of IHD among those with light OPA and higher risk of IHD among those with moderate OPA. The association with IHD among women with moderate OPA had the opposite direction according to hypertension status. However, among hypertensive women, there were only few women with moderate and strenuous OPA and only few cases of IHD (table D in appendix). There was no statistically significant interaction between OPA and hypertension (p= 0.732).

An additional sensitivity analysis of the association between OPA and IHD among those with a low level of vocational training: without or ≤ 1 years of training was performed. Among 623 women and 393 men with a low level of vocational training the age-adjusted association between OPA and IHD was resembling that shown in table 3A at all levels of OPA with even stronger associations among men with moderate (HR 1.59 (95% CI 0.78–3.25)) or strenuous OPA (HR 1.66 (95% CI 0.76–3.61)).

Furthermore, we made a sensitivity analysis with 20 years follow-up time. This analysis showed the same pattern and was comparable to table 3B with a higher risk of IHD among men with higher levels of OPA and a lower risk among women with higher levels of OPA – compared to men and women with sedentary OPA, respectively.

Discussion

Main findings

We aimed to investigate the association between OPA and IHD and to elucidate whether men and women were differently affected.

The association between OPA and IHD differed by sex. Moderate and strenuous OPA was associated with around 45% higher risk of IHD among men and around 65% lower risk of IHD among women, in the fully adjusted model. This difference was observed both in the CI-curves and in the results of the survival analyses. To directly compare the associations in men and women we also presented the results with a common reference group. Compared to women with sedentary OPA, HR for IHD among men was higher in all OPA categories and men with moderate or strenuous OPA had more than two times higher HR for IHD in the age-adjusted analysis.

Comparison with other studies

Two studies, including both sexes, are in accordance with the finding in the present study of an adverse association between high OPA and risk of IHD among men and an indication of a protective effect of high OPA among women compared to those with sedentary work (8, 12). Also, there are studies, among either men or women, in accordance with the present study. Several studies among men showed detrimental effects of high OPA on cardiovascular health (8-12). As well, beneficial effects of OPA, with respect to risk of heart disease and CVD, have been observed among women in previous studies (18, 19).

In contrast, some previous studies among men showed no association between OPA and heart disease or CVD (13, 14) or suggested a protective effect with respect to heart disease (17-19). Among women, a few studies showed (15) or indicated (9, 16) that high OPA was associated with increased risk of heart disease, whereas other studies have shown no association (8, 11, 17). Though there are several studies in accordance with the findings of this study, overall, the findings are mixed.

A general problem with examining the association between OPA and IHD in women, in the working age, is that large populations are needed to have sufficient statistical power, as IHD is a rarer event among women than among men, in the working age (23).

Differences between men and women

The present study is one in very few demonstrating that the association between OPA and IHD differs by sex, shown by the statistically significant interaction between OPA and sex. In accordance, a study from 2013 also showed statistically significant interaction between OPA and sex (9). In contrast, two Danish studies did not find statistically significant interaction between OPA and sex (6, 20). Otherwise, most studies that stratified by sex did not report tests for interaction between OPA and sex, or did not stratify by sex, but merely adjusted for sex. When aiming to establish whether the relationship between OPA and risk of IHD is in fact different in men and women, it is necessary to explore potential effect modification by sex.

Combining the results of examining the association between OPA and IHD among both sexes and the results in strata of sex, demonstrates the importance of exploring sex-differences in studies of health effects of OPA. In the analysis including both men and women the opposite direction of the association between men and women is masked. One of the possible explanations of the sex-difference, in the present study, may be that men and women have different levels of OPA, although their questionnaire answer place them in the same OPA category. There is a high degree of gender segregation in the labor market, especially in jobs with high physical demands (26), and a recent study showed that within sitting, standing and walking occupations, the types of occupational groups were different for men and women (35). Women in jobs with high physical demands are typically working in the health, social care, kitchen or cleaning sectors (26). This is also the case for lifting where a Danish study showed that women exposed to lifting were working in the health or cleaning sector, whereas men exposed to lifting held a variety of jobs (36). Furthermore, even in the case where men and women have the same occupational titles, there are large differences in their physical working conditions (27). In addition, the individual assessment of the physical demands at work in a questionnaire is partly subjective and the answers could be related to the physical capacity and health status of the respondent and may also be relative to colleagues and others in the same profession.

Another possible explanation of the sex-difference in the association between OPA and IHD could be physiological sex-differences. Men and women are different with respect to e.g., muscle mass, physical capacity and sex hormones and these differences may play a role in both the physical impact and perception of a given workload (24, 25). Furthermore, men and women at the same age differ in their vulnerability to heart disease due to a 7 to 10 years later first manifestation of heart diseases in women (23). Among women, menopause, and the following changes in the level of sex hormones and the physiological consequences of this, may affect the association between OPA and IHD. It has been shown that the level of HDL is affected by menopause (37). In the present study, adjustment for HDL affected the association between OPA and IHD in the analysis where women with sedentary OPA was the common reference group.

A preliminary analysis of the association between OPA and IHD stratified by menopause/use of hormone-replacement-therapy (HRT) and adjusted for age indicated that among menopausal women, using HRT, a higher level of OPA was associated with a higher risk of IHD, which was not the case among pre-menopausal or menopausal women not using HRT (results not shown). This emphasizes the importance of taking these factors into account in studies including menopausal women and this finding should be further investigated in studies including more women.

Also, a sensitivity analysis of the association between OPA and IHD stratified for hypertension showed a different pattern among men and women with a higher risk of IHD among hypertensive men with strenuous OPA than among normotensive men and a tendency of a u-shaped association among hypertensive women that also has been observed in a previous study (38). However, some of the strata were rather small and this finding should be further investigated in larger cohorts.

Strengths and weaknesses of the study

The Monica study is a prospective study with a high response rate, it includes a fairly large number of both men and women, and it was therefore possible to explore sex-differences. Information on IHD was obtained in a hospital-based registry, providing valid information on incident IHD (28) with almost complete coverage. Furthermore, this information is independent of information about the level of OPA.

It is a strength that the follow-up time is sufficiently long to obtain the number of cases of IHD necessary for statistical power. However, some workers may retire or change exposure during follow-up. If workers with high OPA to a higher degree than those with light or sedentary OPA change to jobs with less physical demands (the co-called healthy worker selection bias) or retire during follow-up this could bias the results. However, a sensitivity analysis with 20 years follow-up time showed the same pattern as the main analyses. Two studies have shown that the level of OPA is rather stable over time (39, 40). Future studies should investigate the impact of continuity and duration of OPA exposure.

The assessment of OPA is self-reported and based on the well-known Saltin and Grimby question (29), and has been shown to be useful in population studies to divide the population in broad categories of OPA. However, it is a weakness of this question that it is not possible to separate walking and standing work. Standing work for many hours can impose strain on the cardiovascular system and has been shown to be associated with heart disease (35). It would have been interesting to be able to separate these exposures.

The Monica studies were designed for studying risk factors for CVD and therefore many relevant confounders related to risk of IHD are assessed. However, residual confounding from other relevant possible confounders as psychosocial work factors and shift work that were not assessed in the Monica study cannot be ruled out.

The exposure and many of the covariates were assessed by self-report, which may have caused some degree of misclassification. This could dilute the size of the associations and lead to smaller effects.

High OPA is known to be associated with low SES (12, 34) and therefore it is important to take this into account in the analyses. Adjustment for SES only slightly changed the estimates in this study, and the sensitivity analysis of the association between OPA and IHD among those with short vocational training showed similar results as among all participants. This implies that SES is not the underlying explanation of the associations.

As an increased SBP may be in the causal pathway from high OPA to IHD the impact of adjusting for SBP was investigated as a separate analysis. This adjustment had only minor impact on the estimates.

In conclusion, the association between OPA and IHD was different among men and women and this study is one in very few to demonstrate this. Compared to sedentary OPA, demanding or strenuous OPA was associated with a higher risk of IHD among men. In contrast, a higher level of OPA seemed to be protective in relation to IHD compared to sedentary OPA among women. Future studies should investigate the underlying mechanisms for this difference, whether it is differences in exposure and/or physiological differences between the two sexes.

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Authors Contributions:

All authors have:

1. made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data and
2. drafted the article or revised it critically for important intellectual content and
3. given final approval of the version to be published and
4. agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability Statement: Data cannot be shared for ethical/privacy reasons.

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TABLES

Table 1

		All participants (n=3,105)			Women (n=1,399)			Men (n=1,706)		
		n	%	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)
Sociodemographic and socioeconomic factors										
Age	**Mean age**			43.6 (10.3)			42.8 (10.0)			44.2 (10.5)
	30 - 32 years	895	28.8		428	30.6		467	27.4	
	40 - 42 years	920	29.6		430	30.7		490	28.7	
	50 - 52 years	840	27.1		382	27.3		458	26.9	
	60 - 62 years	450	14.5		159	11.3		291	17.1	
Civil status	**Married/cohabitating**	2,621	84.4		1,128	80.6		1,493	87.5	
	Living alone	484	15.6		271	19.4		213	12.5	
Vocational training	**Unskilled**	404	13.0		245	17.5		159	9.3	
	Short (<2 years)	2,249	72.4		992	70.9		1,257	73.7	
	Medium theoretic (3-4 years)	345	11.1		139	9.9		206	12.1	
	Long higher education (>5 years)	107	3.45		23	1.6		84	4.9	
Occupational physical activity										
OPA	**Sedentary**	883	28.4		458	30.7		425	24.9	
	Moderate	1,530	49.3		739	52.8		791	46.4	
	Demanding	526	16.9		176	12.6		350	20.5	
	Strenuous	166	5.4		26	1.9		140	8.2	
Risk factors for IHD										
LTPA	**Moderate/vigorous**	663	21.4		176	12.6		487	28.6	
	Light	1577	50.8		761	54.4		816	47.8	
	Sedentary	865	27.9		462	33,0		403	23.6	
Smoking	**Current**	1,831	59.0		771	55.1		1,060	62.1	
	Former	563	18.1		211	15.1		352	20.6	
	Never	711	22.9		417	29.8		294	17.2	
Alcohol intake*	**Intake Units/week**			9.6 (11.9)			5.11 (6.4)			13.3 (13.9)
Self-rated fitness	**Better than peers**	652	21.1		218	15.6		434	25.5	
	Same as peers	2,184	70.5		1,055	75.5		1,129	66.4	
	Worse than peers	262	8.5		124	8.9		138	8.1	
	Missing	7								
BMI continuous*	**kg/m^2**			24.6 (3.8)			23.6 (4.0)			25.3 (3.5)
Diabetes	**No**	3,046	98.1		1,380	98.6		1,666	97.6	
	Yes	59	1.9		19	1.4		40	2.4	
AMI/other heart disease close relatives	**No**	2,208	72.1		958	69.5		1,250	74.2	
	Yes	856	27.9		421	30.5		435	25.8	
	Missing	41								
Blood lipids*	**Total cholesterol (mmol/l)**			6.02 (1.22)			5.90 (1.2)			6.1 2(1.23)
	HDL cholesterol (mmol/l)			1.49 (0.42)			1.66 (0.42)			1.35 (0.37)
	Plasma triglyceride (mmol/l)			134.3 (111.6)			109.5 (56.4)			155.4 (138.1)
Blood pressure	**Systolic blood pressure (mmHg)**	3,105		122.6 (16.1)	1,399		119 (16.1)	1,706		125.5 (15.4)
	Diastolic blood pressure (mmHg)	3,105		76.8(11.0)	1,399		73.8 (10.6)	1,706		79.3 (10.6)
Hypertension$^{\#}$	**No**	2,266	73		1,069	76.4		1,197	70.2	
	Yes	839	27		330	23.6		509	29.8	
Occupational factors										
Working time	**Hours/week**	3,097		38.3 (9.8)			32.9 (9.8)			42.6 (7.4)
	Missing	8								

Table 2

OPA	n/no with IHD	Model A HR	Model A 95% CI	Model B HR	Model B 95% CI	Model C HR	Model C 95% CI
Sedentary	883/133	1		1		1	
Light	1,530/250	1.03	0.83 to 1.27	1.03	0.83 to 1.26	0.99	0.80 to 1.23
Moderate, some lifting	526/97	1.34	1.03 to 1.74	1.23	0.94 to 1.59	1.15	0.87 to 1.52
Strenuous, heavy lifting	166/30	1.49	1.00 to 2.22	1.18	0.79 to 1.75	1.14	0.75 to 1.74

Table 3A

			Model 1		Model 2		Model 3		Model 4	
Sex	**OPA**	No. of subjects/no. with IHD	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Women	Sedentary	458 (57)	1		1		1		1	
	Light	739 (74)	0.72	0.51 to 1.02	0.74	0.52 to 1.04	0.68	0.48 to 0.97	0.67	0.47 to 0.96
	Moderate, some lifting	176 (-)#	0.83	0.50 to 1.38	0.86	0.52 to 1.44	0.77	0.46 to 1.29	0.77	0.46 to 1.30
	Strenuous, heavy lifting	26 (-)#	0.35	0.05 to 2.55	0.37	0.05 to 2.68	0.30	0.04 to 2.17	0.30	0.04 to 2.17
Men	Sedentary	425 (76)	1		1		1		1	
	Light	791 (176)	1.25	0.96 to 1.64	1.27	0.97 to 1.66	1.23	0.93 to 1.61	1.22	0.93 to 1.61
	Moderate, some lifting	350 (77)	1.49	1.08 to 2.05	1.54	1.12 to 2.12	1.40	1.01 to 1.94	1.42	1.01 to 1.98
	Strenuous, heavy lifting	140 (29)	1.45	0.94 to 2.22	1.48	0.97 to 2.28	1.44	0.92 to 2.26	1.46	0.93 to 2.29
Interaction sex * OPA			p=0.048		p=0.052		p=0.032		p=0.032	

Table 3B

			Model 1		Model 2		Model 3		Model 4	
Sex	**OPA**	No. of subjects/no. with IHD	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Women	Sedentary	458 (57)	1		1		1		1	
	Light	739 (74)	0.72	0.51 to 1.02	0.74	0.52 to 1.04	0.68	0.48 to 0.97	0.67	0.47 to 0.96
	Moderate, some lifting	176 (-)#	0.83	0.50 to 1.38	0.86	0.52 to 1.44	0.77	0.46 to 1.29	0.77	0.46 to 1.30
	Strenuous, heavy lifting	26 (-)# *	0.35	0.05 to 2.55	0.37	0.05 to 2.68	0.30	0.04 to 2.17	0.30	0.04 to 2.17
Men	Sedentary	425 (76)	1.48	1.05 to 2.08	1.57	1.11 to 2.21	0.99	0.68 to 1.47	0.99	0.67 to 1.46
	Light	791 (176)	1.85	1.37 to 2.50	1.99	1.47 to 2.70	1.22	0.87 to 1.72	1.21	0.85 to 1.71
	Moderate, some lifting	350 (77)	2.20	1.56 to 3.1	2.42	1.71 to 3.42	1.39	0.94 to 2.06	1.40	0.95 to 2.06
	Strenuous, heavy lifting	140 (29)	2.14	1.37 to 3.35	2.32	1.48 to 3.64	1.44	0.88 to 2.35	1.44	0.88 to 2.36

Figure legends

Figure 1. Flowchart of participants in the Monica Study and formation of the study population.

Figure 2a and b. The cumulative incidence curves for hazard of both IHD at any given time during follow-up from baseline to end of follow-up among a. women and b. men.

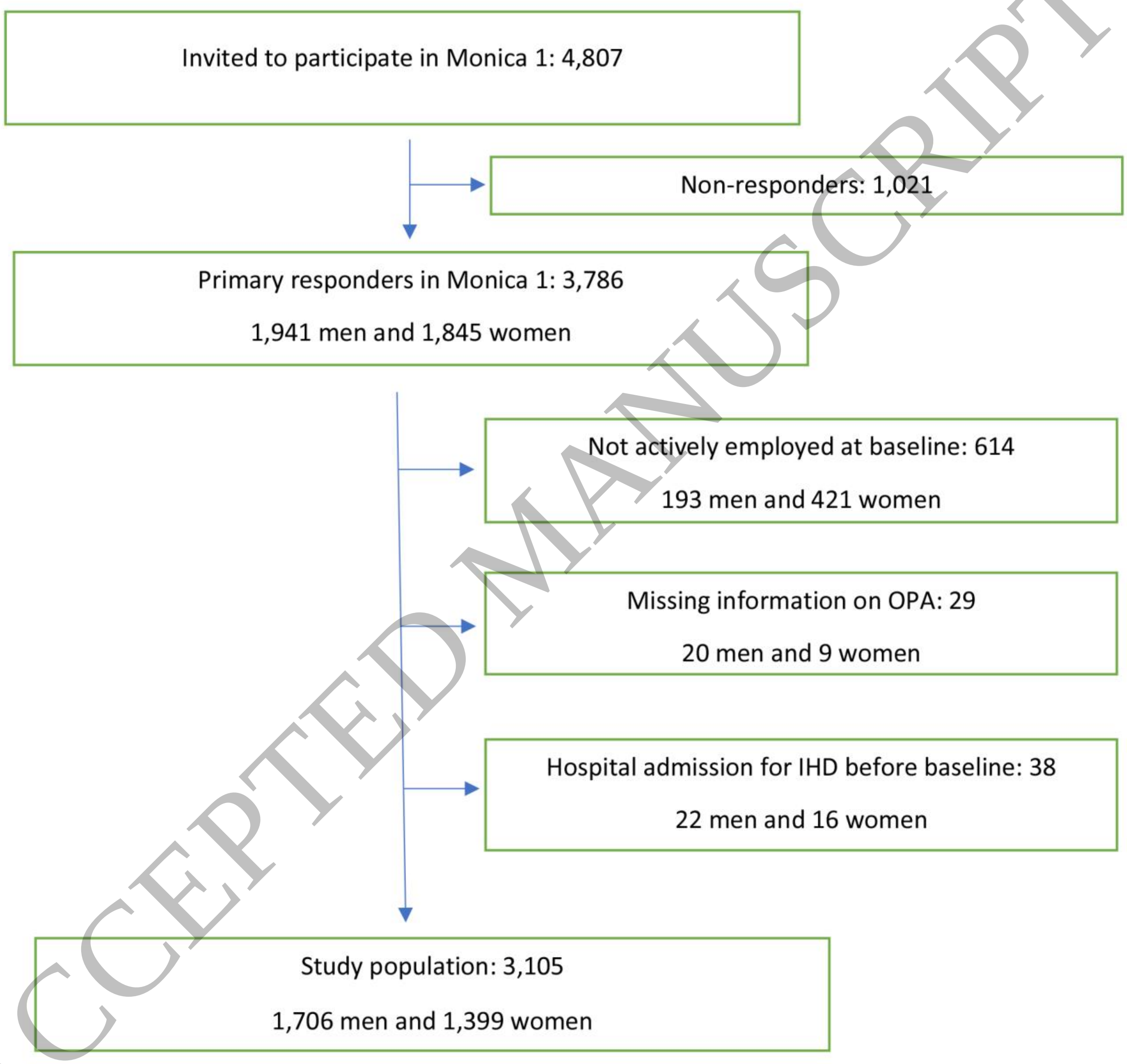
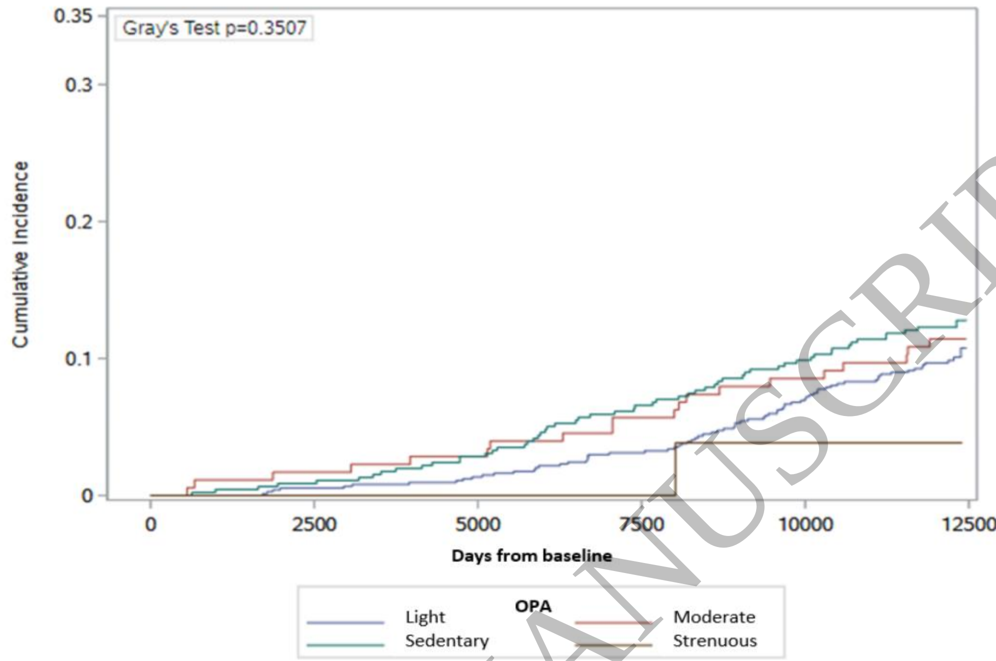


Figure 1
166x179 mm (19 x DPI)

a. Women



b. Men

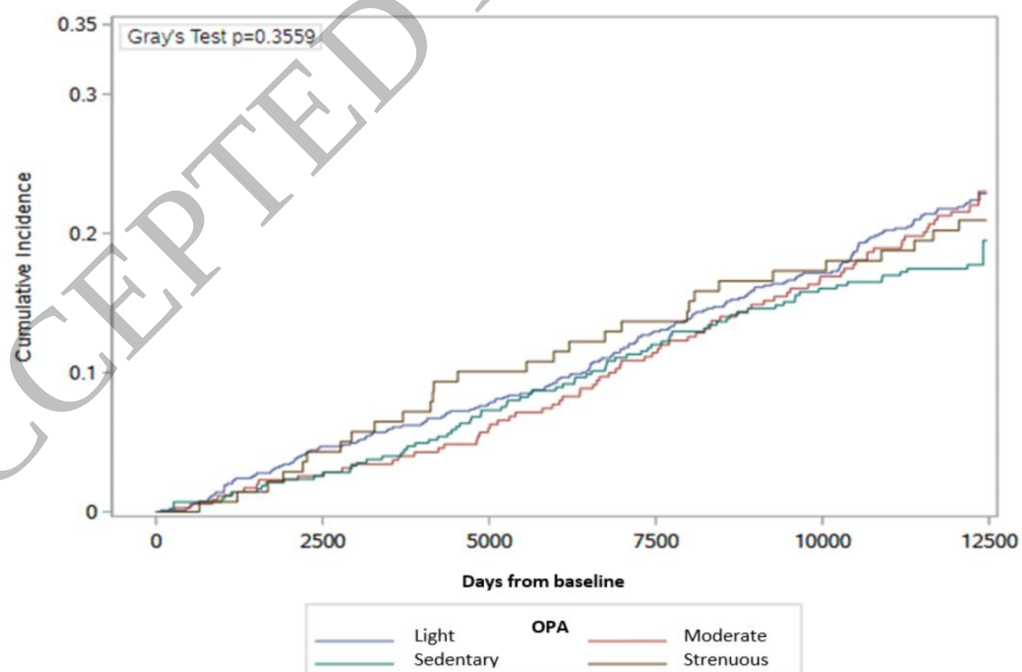


Figure 2a and b
143x222 mm (19 x DPI)