



Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study

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4 **Occupational and leisure time physical activity:**
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6 **risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study**
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ABSTRACT

Objectives Men with low physical fitness and high occupational physical activity are recently shown to have an increased risk of cardiovascular disease and all-cause mortality. The association between occupational physical activity with cardiovascular disease and all-cause mortality may also depend on leisure time physical activity.

Design 7,819 males and females aged 25-66 years without history of cardiovascular disease who attended an initial examination in the Copenhagen City Heart Study in 1976-78 were followed for myocardial infarction and all-cause mortality until 2010. Occupational physical activity was defined by combining information from baseline (1976-78) with re-assessment in (1981-83). Conventional risk factors were controlled for in Cox analyses.

Results During the follow-up, 2,888 subjects died from all-cause mortality and 787 had a first event of myocardial infarction. Overall, occupational physical activity predicted all-cause mortality and myocardial infarction in men, but not in women (test for interaction $p=0.02$). Among males, high occupational physical activity was associated with an increased risk of all-cause mortality among those with low and moderate leisure time physical activity (Hazard ratio (HR) =1.56; 95% confidence interval (95%CI) 1.11-2.18) and (HR=1.31; 95%CI 1.05-1.63), but not among males with high leisure time physical activity (HR=1.00; 95%CI 0.78-1.26) (test for interaction $p=0.04$). Similar, but weaker tendencies were found for myocardial infarction. Among women, OPA was not associated with subsequent all-cause mortality or MI.

Conclusions The findings suggest that high leisure time physical activity perhaps through increased physical fitness yields protection against harmful effects of high occupational physical activity among men.

ARTICLE SUMMARY

Article focus

- Men with low physical fitness and high occupational physical activity are recently shown to have an increased risk of cardiovascular disease and all-cause mortality.
- It is unknown if the association between occupational physical activity with cardiovascular disease and all-cause mortality also depends on leisure time physical activity.

Key messages

- This study shows that men with high occupational physical activity have an increased risk of all-cause mortality.
- Leisure time physical activity was found to modify the positive association between occupational physical activity and risk of all-cause mortality
- Men with high occupational physical activity ought to be recommended and given the possibility to be highly physically active during leisure time

Strengths and limitations

Study strengths include the long follow-up time, repeated assessment of the occupational physical activity, objective measures of several covariates from clinical examinations, and information on outcomes obtained from valid registers, and participation of both genders. Some limitations are the lack of control for psychosocial work factors and the self-assessed exposures.

INTRODUCTION

A positive association has been demonstrated between occupational physical activity and risk of cardiovascular and all-cause mortality among men with low cardiorespiratory capacity, i.e. physical fitness [1]. A physiological explanation may be prolonged intravascular turbulence and increased wall shear stress from occupational physical activity several hours per day [2], inducing inflammatory processes in the arterial walls eventually leading to atherosclerosis [3].

Theoretically, these acute adverse effects of occupational physical activity may be modified by leisure time physical activity known to promote cardio-respiratory fitness [4] and reduce heart rate and blood pressure during daily activities [5]. A higher cardio-respiratory fitness and lower heart rate provides a longer period in the diastolic phase of the cardiac cycle, causing better myocardium perfusion and reduced intravascular turbulence and wall shear stress, lowering the risk of inflammation and atherosclerosis [2, 3]. We have previously shown that high occupational physical activity confers an increased risk of cardiovascular and all-cause mortality among men with a low physical fitness, but not among men with high physical fitness [1]. However, the role of leisure time physical activity on the risk for cardiovascular disease and mortality from high occupational physical activity remains unsettled.

Relatively few studies have investigated the effects of occupational physical activity on cardiovascular disease and mortality among females [6]. Because type of occupational physical activity differs between male and female occupations [7] the effects of occupational physical activity on cardiovascular health may be different between the genders. A recent editorial on occupational physical activity and cardiovascular health highlights the need for future investigations in additional cohorts among both genders [8].

Accordingly, we hypothesized that high occupational physical activity is an independent risk factor for myocardial infarction and all-cause mortality in both men and women. Finally, we hypothesized that the level of leisure time physical activity in both genders modifies the association between occupational physical activity and risk of myocardial infarction and all-cause mortality.

MATERIALS AND METHODS

Study population

The Copenhagen City Heart Study is a prospective cardiovascular population study comprising a random sample of 19,698 males and females aged 20 to 101 years, drawn from the Copenhagen Population Register as of January 1, 1976. The first survey lasted from 1976 to 1978 (response rate 74%) and the second from 1981 to 1983 (response rate 70%). A total of 11,135 persons participated in both examinations.

Participants with previous myocardial infarction or stroke by self-report or according to the Danish National Patient Register established in 1977 were excluded (n= 644). Moreover, all persons above the age of retirement in Denmark at the time of the second examination (i.e. 67 years of age) were excluded, leaving 8,496 persons eligible. Finally, we excluded the 677 persons with missing values in occupational physical activity in one of the surveys, leaving 7,819 eligible for analyses.

Established cardiovascular risk factors were assessed at both examinations using a self-administered questionnaire and a physical examination. The Ethics Committee for the Copenhagen area approved the study (KF 100.2039/91).

Occupational physical activity (the main predictor variable)

A single question with four categories was applied for measuring occupational physical activity: 'Which description most precisely covers your pattern of physical activity at work? [9]

1. You are mainly sedentary and do not walk much around at your workplace. *E.g.* desk work, work including assembling of minor parts. [Score 1]
2. You walk around quite a bit at your workplace but do not have to carry heavy items. *E.g.* light industrial work, non-sedentary office work, inspection and the like. [Score 2]

3. Most of the time you walk, and you often have to walk up stairs and lift various items. Examples include mail delivery and construction work. [Score 3]
4. You have heavy physical work. You carry heavy burdens and carry out physically strenuous work. *E.g.* work including digging and shoveling. [Score 4]

To reduce risk of misclassification, the main predictor variable was based on combined information from assessment in 1976-78 and 1981-83, summarizing and categorizing scores into: “low” = score 2-3, “moderate” = score 4-5, and “high” = score 6-8.

Leisure time physical activity (the potential effect modifier)

A single question with four categories was applied for measuring leisure time physical activity:

‘Which description most precisely covers your pattern of physical activity during leisure time? [10]

1. Being almost entirely sedentary (e.g., reading, watching television or movies, engaging in light physical activity such as walking or biking for less than 2 hours per week). [Score 1]
2. Engaging in light physical activity for 2–4 hours per week. [Score 2]
3. Engaging in light physical activity for more than 4 hours per week or more vigorous activity for 2–4 hours per week (e.g., brisk walking, fast biking, heavy gardening, sports that cause perspiration or exhaustion). [Score 3]
4. Engaging in highly vigorous physical activity for more than 4 hours per week or regular heavy exercise or competitive sports several times per week. [Score 4]

Because of very few females (n=52) and males (n=140) in the highest category of leisure time physical activity, the variable was categorised into: score 1 = “low”, score 2 = “moderate”, and score 3-4 = “high”.

Potential confounders

Potentially confounding factors for the association between occupational physical activity and cardiovascular health and mortality were measured as follows: smoking habits were categorized into never smokers, ex-smokers, and current smokers of <15, ≥15 g of tobacco per

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4 day. Current tobacco consumption was calculated by equating a cigarette to 1 g of tobacco, a cheroot to 3 g of tobacco, and a cigar to 5 g of
5 tobacco. Systolic blood pressure was measured in a sitting position after 5 minutes of rest. Diabetes and treatment for hypertension were
6 self-reported. Body mass index (BMI) was calculated as measured weight (kg) divided by height squared (m²). Alcohol consumption was
7 categorized as abstention, monthly, weekly, or daily intake. Household income was self-reported, and stratified into low, medium and high.
8 Cholesterol was measured non-fasting in mmol/L.
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12 13 14 **Follow-up**

15 Subjects were followed in national registers from the second examination (1981-83) until December 2008 for myocardial infarction and
16 May 2010 for all-cause mortality. The end-point myocardial infarction was defined as the first incidence of fatal or non-fatal myocardial
17 infarction according to the International Classification of Diseases: 8th revision code 410, and 10th revision codes I21–I22. Episodes of
18 non-fatal myocardial infarction were retrieved from The National Hospital Discharge Register. Deaths were obtained from The Civil
19 Registration System and causes of death from The National Register of Causes of Death. To reduce the maximum follow-up time without
20 exposure to occupational physical activity to 10 years (the pension age is 67 years in Denmark), persons were censored from follow-up
21 analyses at 77 years of age. Subjects were thus followed until outcome, age 77 or end of follow-up in 2010, whatever came first. The
22 median duration of follow-up was 17.8 years (range 0 - 27.7) for myocardial infarction and 18.4 years (range 0 - 29.4) for all-cause
23 mortality.
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32 **Analyses**

33 For demographics, Pearson's chi-square test was used for categorical covariates and one-way ANOVA for continuous covariates.
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37 The associations between occupational physical activity and fatal and non-fatal myocardial infarction, and all-cause mortality were studied
38 using sex-specific Cox proportional hazards regression models. Associations were investigated both overall and stratified according to level
39 of leisure time physical activity. The Cox models were performed with age as underlying time scale and age at baseline as entry time. All
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4 adjusted models included the covariates smoking, alcohol consumption, BMI, leisure time physical activity, systolic blood pressure,
5 diabetes, blood pressure medication and household income. We tested for interaction between gender, occupational physical activity, and the
6 outcomes all-cause mortality and myocardial infarction. P-values below 0.05 were considered statistically significant. Statistical analyses
7 were performed with R version 2.13.1.
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12 Moreover, we tested for interaction between occupational physical activity, leisure time physical activity, and the outcomes all-cause
13 mortality and myocardial infarction.
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17 Two additional analyses were performed. In the first analysis, the risk of all-cause mortality and myocardial infarction was investigated
18 including exclusively males and females who had not changed their level of occupational physical activity from the first (1976-78) to the
19 second examination (1981-83). Due to the low number of females in the highest category of occupational physical activity (n=2), the
20 variable was categorized as: “low” = score 1, “moderate” = score 2, and “high” = scores 3 and 4 pooled. Because of the strong association
21 between occupational physical activity and years of education, we found it necessary to carry out a second additional analysis including
22 only those with a maximum school length of 10 years.
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RESULTS

A total of 1,493 (41.4%) males and 1,395 (28.5%) females died; 511 (14.2%) males and 276 (5.6%) females experienced a first myocardial infarction episode during the follow-up period.

Table 1 shows lifestyle and other characteristics according to level of occupational physical activity among males and females. Several significant differences were found, but differences were generally small with no clear positive or negative trends. However, men with high occupational physical activity were more frequently smokers, had higher BMI, fewer with hypertension, and fewer with long (> 10 years) school education. Among females, women with high occupational physical activity had lower alcohol consumption, a lower leisure time physical activity level, lower systolic blood pressure, and fewer had a long school education.

Table 2 shows the distribution of participants in the four groups of occupational physical activity among males and females without a history of cardiovascular disease at the first examination (1976-78) and the second examination (1981-83) in the Copenhagen City Heart Study. Level of occupational physical activity remained constant between the two examinations in 61.0%, decreased in 22.6% and increased in 16.4%.

Table 3 shows the association between occupational physical activity and risk of all-cause mortality and myocardial infarction stratified by gender. The occupational physical activity variable consisted of the combined measure of occupational physical activity in 1976-78 and 1981-83. Among males, the risk of myocardial infarction increased with increasing occupational physical activity but only significantly among men with moderate exposure. For all-cause mortality, occupational physical activity increased the risk in a dose-response manner. Males with moderate occupational physical activity had an increased risk of 15% while those with high occupational physical activity had a 22% increase in all-cause mortality referencing males with low occupational physical activity. Among females, no tendency was found that increasing occupational physical activity increased the risk of either all-cause mortality or myocardial infarction.

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4 The association between occupational physical activity and both outcomes differed by gender even after control for potential confounders,
5 test for interaction being significant ($p=0.02$) for both all-cause mortality and myocardial infarction.
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9 In the additional analysis comprising only participants with unchanged level of occupational physical activity from the first (1976-78) to
10 the second examination (1981-83), i.e. those shown in bold in Table 2 ($n=4,766$), the risk estimates did not differ materially from the
11 original model including all participants (data not shown).
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15 Table 4 shows the association between the combined measure of occupational physical activity and risk of all-cause mortality and
16 myocardial infarction stratified by leisure time physical activity among males and females. Among men with low or moderate leisure time
17 physical activity, risk of all-cause mortality was higher with increasing occupational physical activity. However, among men who were
18 highly physically active during leisure time, the risk of all-cause mortality was independent of occupational physical activity level. Test for
19 trend showed a significant interaction between occupational and leisure time physical activity ($p=0.04$) even after control for potential
20 confounders. Similar tendencies, although non-significant, were found for myocardial infarction among males. Among females,
21 occupational physical activity did not increase either the risk of all-cause mortality or myocardial infarction in any of the leisure time
22 physical activity groups and no significant interaction was found.
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31 In the additional analysis including only those with a maximum school length of 10 years, the multi-adjusted analyses among males
32 showed a significant increased risk of all-cause mortality from moderate ($HR=1.17$; $95\%CI=1.00-1.37$) and high ($HR=1.21$; $95\%CI=1.03-$
33 1.42) occupational physical activity, but no significantly increased risk for myocardial infarction from moderate ($HR=1.27$; $95\%CI=0.98-$
34 1.65) and high ($HR=1.11$; $95\%CI=0.85-1.46$) occupational physical activity. Among females with a maximum school length of 10 years,
35 occupational physical activity was not significantly associated with all-cause mortality or myocardial infarction.
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COMMENTS

The primary finding of this study was the observation that leisure time physical activity modifies the positive association between occupational physical activity and risk of all-cause mortality. The second observation relating to the aim of the present study was the clear difference between males and females regarding occupational physical activity as a predictor of all-cause mortality and myocardial infarction. Overall, occupational physical activity did not predict risk among women. The third finding was that, overall, among men with a high occupational physical activity a statistically significant increased risk of all-cause mortality was seen, also when controlling for relevant confounders. Regarding myocardial infarction risk, the results were less clear but with similar tendencies.

The observations of the present study are in agreement with a number of previous studies addressing the association between high occupational physical activity and increased risk of all-cause mortality and cardiovascular disease [3, 6, 11-13]. The observation of a modifying effect of leisure time physical activity is in agreement with our previous observation that a high physical fitness seemed to completely counteract the positive association between occupational physical activity and risk of all-cause mortality and even ischaemic heart disease mortality [1].

Physical activity is regarded as beneficial for cardiovascular health but a distinction should be made between leisure time and occupational physical activity (Holtermann et al 2009). In contrast to leisure time physical activity, most occupational physical activity in modern industrialized societies does not include activities with high enough intensity to increase the maximal oxygen uptake capacity (physical fitness) (Holtermann et al 2010). Such activities encompass regular dynamic use of large muscle groups with high intensity and sufficient time for recovery [14, 15]. An explanation for the increased risk of mortality attributed to high occupational physical activity may include hemodynamic effects on the cardiovascular system promoting the development of atherosclerosis [2]. Several hours per day of high levels of occupational physical activity will inevitably cause prolonged elevated heart rate, eliciting a higher fraction of the cardiac cycle in the systolic phase with unfavorable intravascular turbulence and wall shear stress, leading to inflammatory processes in the arterial walls, which may result in atherosclerosis, cardiovascular disease and death [3].

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As illustrated in table 2, most study participants did not change their level of occupational physical activity from the first examination (1976-78) to the second examination (1981-83). Among the 39% who did, changes were typically small and mostly to lower levels of occupational physical activity. Additional analyses on the association between occupational physical activity and all-cause mortality and myocardial infarction exclusively including participants who reported the same level of occupational physical activity at both examinations, showed results that were practically identical with the analyses based on the entire study population (data not shown). So, it seems unlikely that the observed positive association between occupational physical activity and all-cause mortality as well as myocardial infarction can be attributed to occupational physical activity changes due to health problems. Moreover, the significantly increased multi-adjusted risk of all-cause mortality from high occupational physical activity among males with a low educational level (<10 years) indicates that the observed association between occupational physical activity and all-cause mortality not is a result of socioeconomic confounding.

In contrast to the significant relationship among men, occupational physical activity was not a predictor of either all-cause mortality or myocardial infarction among women. The most likely reason for this difference is the fact that occupational physical activity qualitatively and quantitatively may reflect different physiological impacts from male and female works tasks, respectively. Lifting of heavy burdens, i.e. isometric work is a much more frequent work task in male occupations, and more dynamic work tasks more frequently characterize manual female work demands [7]. It is well known that heavy isometric work induces an acute rise in blood pressure with a subsequent induction of arterial wall shear stress. Due to the more dynamic occupational work tasks for females, this physiological effect may not be nearly as pronounced as for males.

Strengths and limitations

The main strengths of the present study include the long follow-up time, repeated assessment of the occupational physical activity, objective measures of several covariates from clinical examinations, and information on outcomes obtained from valid registers, and

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4 participation of both genders. Some limitations of the study should be addressed: 1) the lack of control for psychosocial work factors, and
5 2) exposures are self-assessed. Ad 1) Previous studies have shown that control for psychosocial work factors have minimal influence on the
6 association between occupational physical activity and cardiovascular disease and mortality [3, 6]. Ad 2) Another limitation of the present
7 study is that the occupational physical activity and leisure time physical activity information was based on self-assessment, which may
8 entail some degree of misclassification [16]. Such misclassification would however not explain the findings presented, rather the
9 associations might have been attenuated.
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16 In conclusion, occupational physical activity was a predictor of all-cause mortality as well as myocardial infarction in men, but not in
17 women. Occupational physical activity was positively associated with risk of all-cause mortality in males with low and moderate leisure
18 time physical activity, but not in males with high leisure time physical activity. The results suggest that high leisure time physical activity
19 perhaps through increased physical fitness yields protection against harmful effects of high occupational physical activity. Gender
20 differences in the relationship between occupational physical activity and risk of all-cause mortality and myocardial infarction may reflect
21 qualitative as well as quantitative differences with respect to occupational physical exposures.
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TABLES

Table 1. Demographic and lifestyle factors of males and females between 20 and 67 years of age without a history of cardiovascular disorders stratified by level of occupational physical activity from the second examination (1981-83) in the Copenhagen City Heart Study, n=7,819. P-values of differences between the groups of occupational physical activity are provided.

Gender:	Males				Females			
	Low n = 1,114	Moderate n = 1,152	High n = 1,015	p-value	Low n = 1,506	Moderate n = 2,303	High n = 729	p-value
Occupational physical activity								
Age, mean (SD)	52.1 (10.2)	53.0 (9.4)	51.5 (8.6)	<0.001	54.1 (9.1)	54.4 (9.0)	49.7 (9.1)	<0.001
BMI, mean (SD)	25.6 (3.9)	26.0 (3.7)	26.6 (3.7)	<0.001	24.5 (4.3)	24.9 (4.6)	24.8 (4.3)	0.04
Current smokers, %	62.9	65.7	69.1	<0.01	55.6	54.0	59.8	0.02
Consuming ≥1 unit alcohol a day, %	34.8	32.9	41.5	<0.001	13.4	10.8	7.1	<0.001
Low leisure time physical activity, %	14.9	11.8	14.3	<0.001	16.5	13.4	11.0	<0.001
Systolic blood pressure, mean (SD)	140.4 (19.4)	140.9 (19.5)	139.1 (18.8)	0.08	135.2 (20.9)	136.8 (20.6)	131.1 (19.6)	<0.001
Blood pressure medication, %	8.7	7.6	5.4	0.01	9.6	9.2	7.1	0.15
Diabetes, %	4.0	3.7	3.7	0.91	1.5	1.7	1.0	0.36
Low income, %	9.3	12.2	9.0	<0.001	18.5	27.7	17.2	<0.001
High school education (>10 years), %	37.3	17.1	3.8	<0.001	20.6	12.8	10.8	<0.001
Cholesterol, mmol/L	5.7 (1.1)	5.8 (1.1)	5.8 (1.1)	0.40	6.0 (1.2)	6.0 (1.2)	5.8 (1.2)	<0.001

Table 2. Distribution of participants in the four levels of occupational physical activity among males and females between 20 and 67 years of age without a history of cardiovascular disorders at the first examination (1976-78) and the second examination (1981-83) in the Copenhagen City Heart Study, n=7,819. Numbers in bold are those males and females who did not change their level of occupational physical activity from the first (1976-78) to the second examination (1981-83).

Gender	Males				Females			
	Low (1981-83)	Moderate (1981-83)	High (1981-83)	Very high (1981-83)	Low (1981-83)	Moderate (1981-83)	High (1981-83)	Very high (1981-83)
Occupational physical activity								
Low (1976-78)	698	188	51	7	797	347	62	0
Moderate (1976-78)	228	536	191	13	362	1,304	352	2
High (1976-78)	108	201	513	64	117	468	704	5
Very high (1976-78)	58	67	146	212	0	5	11	2

Table 3. Combined measure of occupational physical activity from 1976-78 and 1981-83 as predictor for fatal and non-fatal myocardial infarction and all-cause mortality among males and females between 20 and 67 years of age without a history of cardiovascular disorders in the Copenhagen City Heart Study (n=7,819).

	No. of cases (%)	Hazard Ratio (95% CI) ^a	Hazard Ratio (95% CI) ^b
Males			
<i>Myocardial infarction</i>			
Occupational physical activity			
Low (n=1,114)	133 (12%)	1 (reference)	1 (reference)
Moderate (n=1,152)	183 (16%)	1.34 (1.07-1.68)**	1.30 (1.03-1.64)*
High (n=1,015)	145 (14%)	1.18 (0.93-1.50)	1.20 (0.93-1.55)
<i>All-cause mortality</i>			
Occupational physical activity			
Low (n=1,114)	395 (35%)	1 (reference)	1 (reference)
Moderate (n=1,152)	478 (41%)	1.17 (1.02-1.33)*	1.15 (1.01-1.33)*
High (n=1,015)	435 (43%)	1.21 (1.05-1.38)**	1.22 (1.05-1.41)**
Females			
<i>Myocardial infarction</i>			
Occupational physical activity			
Low (n=1,506)	87 (6%)	1 (reference)	1 (reference)
Moderate (n= 2,303)	113 (5%)	0.82 (0.62-1.09)	0.76 (0.56-1.02)
High (n=729)	45 (6%)	1.10 (0.76-1.57)	0.98 (0.67-1.44)
<i>All-cause mortality</i>			
Occupational physical activity			
Low (n=1,506)	439 (29%)	1 (reference)	1 (reference)
Moderate (n= 2,303)	619 (27%)	0.89 (0.79-1.01)	0.88 (0.78-1.00)
High (n=729)	194 (27%)	0.96 (0.81-1.14)	0.95 (0.79-1.13)

^a: Control made for age

^b: Control made for age, smoking, alcohol, BMI, leisure time physical activity, systolic blood pressure, diabetes, cholesterol, blood pressure medication and household income

*: $p \leq 0.05$, **: $p \leq 0.01$

Table 4. Combined measure of occupational physical activity from 1976-78 and 1981-83 as predictor for fatal and non-fatal myocardial infarction and all-cause mortality among males and females between 20 and 67 years of age without a history of cardiovascular disorders stratified on leisure time physical activity in 1981-83 in the Copenhagen City Heart Study (n=7,819).

	Occupational physical activity		No. of cases (%)	Hazard Ratio (95% CI) ^a	Hazard Ratio (95% CI) ^b
Males					
<i>Myocardial infarction</i>					
Low leisure time physical activity (n=447)	Low	(n=166)	25 (15%)	1 (reference)	1 (reference)
	Moderate	(n=136)	25 (18%)	1.28 (0.74-2.23)	1.39 (0.76-2.53)
	High	(n=145)	23 (16%)	1.15 (0.65-2.03)	1.15 (0.62-2.13)
Moderate leisure time physical activity (n=1,468)	Low	(n=531)	59 (11%)	1 (reference)	1 (reference)
	Moderate	(n=532)	82 (15%)	1.39 (1.00-1.95)	1.27 (0.89-1.80)
	High	(n=405)	63 (16%)	1.43 (1.00-2.04)*	1.41 (0.96-2.06)
High leisure time physical activity (n=1,364)	Low	(n=417)	49 (12%)	1 (reference)	1 (reference)
	Moderate	(n=483)	75 (16%)	1.31 (0.92-1.88)	1.27 (0.87-1.86)
	High	(n=464)	59 (13%)	1.00 (0.69-1.47)	1.04 (0.69-1.55)
<i>All-cause mortality</i>					
Low leisure time physical activity (n=447)	Low	(n=166)	74 (45%)	1 (reference)	1 (reference)
	Moderate	(n=136)	73 (54%)	1.27 (0.92-1.75)	1.15 (0.81-1.62)
	High	(n=145)	85 (59%)	1.48 (1.08-2.02)*	1.56 (1.11-2.18)*
Moderate leisure time physical activity (n=1,468)	Low	(n=531)	185 (35%)	1 (reference)	1 (reference)
	Moderate	(n=532)	230 (43%)	1.24 (1.02-1.50)*	1.28 (1.05-1.57)*
	High	(n=405)	179 (44%)	1.29 (1.05-1.59)*	1.31 (1.05-1.63)*
High leisure time physical activity (n=1,364)	Low	(n=417)	136 (33%)	1 (reference)	1 (reference)
	Moderate	(n=483)	174 (36%)	1.08 (0.86-1.35)	0.96 (0.76-1.22)
	High	(n=464)	171 (37%)	1.06 (0.85-1.33)	1.00 (0.78-1.26)
Females					
<i>Myocardial infarction</i>					
Low leisure time physical activity (n=637)	Low	(n=248)	17 (7%)	1 (reference)	1 (reference)
	Moderate	(n=309)	18 (6%)	0.82 (0.42-1.59)	1.03 (0.49-2.15)
	High	(n=80)	7 (9%)	1.13 (0.47-2.73)	1.55 (0.55-4.35)
Moderate leisure time physical activity (n=2,568)	Low	(n=899)	58 (6%)	1 (reference)	1 (reference)
	Moderate	(n=1,317)	63 (5%)	0.72 (0.50-1.03)	0.65 (0.45-0.95)*
	High	(n=352)	22 (6%)	1.01 (0.62-1.65)	0.78 (0.46-1.33)
High leisure time physical activity (n=1,332)	Low	(n=358)	12 (3%)	1 (reference)	1 (reference)
	Moderate	(n=677)	32 (5%)	1.38 (0.71-2.68)	1.00 (0.49-2.01)
	High	(n=297)	16 (5%)	1.75 (0.82-3.70)	1.18 (0.54-2.60)
<i>All-cause mortality</i>					
Low leisure time physical activity (n=637)	Low	(n=248)	94 (38%)	1 (reference)	1 (reference)
	Moderate	(n=309)	106 (34%)	0.87 (0.66-1.14)	0.89 (0.66-1.20)
	High	(n=80)	30 (38%)	0.91 (0.60-1.37)	0.99 (0.63-1.54)

Moderate leisure time physical activity (n=2,568)	Low	(n=899)	259 (29%)	1 (reference)	1 (reference)
	Moderate	(n=1,317)	325 (25%)	0.83 (0.70-0.98)*	0.80 (0.68-0.95)*
	High	(n=352)	90 (26%)	0.93 (0.73-1.18)	0.92 (0.71-1.18)
High leisure time physical activity (n=1,332)	Low	(n=358)	86 (24%)	1 (reference)	1 (reference)
	Moderate	(n=677)	188 (28%)	1.12 (0.87-1.45)	1.06 (0.81-1.39)
	High	(n=297)	74 (25%)	1.18 (0.86-1.61)	1.05 (0.76-1.45)

^a: Control made for age

^b: Control made for age, smoking, alcohol, BMI, leisure time physical activity, systolic blood pressure, diabetes, cholesterol, blood pressure medication and household income

*: $p \leq 0.05$, **: $p \leq 0.01$

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40 corresponding author at aho@nrcwe.dk. Consent was not obtained, but the presented data are
41 anonymised and risk of identification is very low. No additional data available.
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44 **ORIGINALE STUDY PROTOCOL** It does not exist
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46 **CONTRIBUTORS AND NAME OF GUARANTOR**

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48 All authors contributed to the conception, design, interpretation of data, and writing or critically
49 revising the manuscript. Jacob Louis Marott made the statistical analyses. Andreas Holtermann and
50 Jacob Louis Marott are guarantors
51

52 **ETHICAL APPROVAL**

53 The Ethics Committee for the Copenhagen area Denmark approved the study (KF 100.2039/91).
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

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Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study

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4 **Occupational and leisure time physical activity: risk of all-cause mortality and**
5 **myocardial infarction in the Copenhagen City Heart Study. A prospective**
6 **cohort study**
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ABSTRACT

Objectives Men with low physical fitness and high occupational physical activity are recently shown to have an increased risk of cardiovascular disease and all-cause mortality. The association between occupational physical activity with cardiovascular disease and all-cause mortality may also depend on leisure time physical activity.

Design A prospective cohort study.

Setting The Copenhagen City Heart Study.

Participants 7,819 males and females aged 25-66 years without history of cardiovascular disease who attended an initial examination in the Copenhagen City Heart Study in 1976-78.

Outcome measures Myocardial infarction and all-cause mortality.

Occupational physical activity was defined by combining information from baseline (1976-78) with re-assessment in (1981-83). Conventional risk factors were controlled for in Cox analyses.

Results During the follow-up from 1976-78 until 2010, 2,888 subjects died from all-cause mortality and 787 had a first event of myocardial infarction. Overall, occupational physical activity predicted all-cause mortality and myocardial infarction in men, but not in women (test for interaction $p=0.02$). Among males, high occupational physical activity was associated with an increased risk of all-cause mortality among those with low and moderate leisure time physical activity (Hazard ratio (HR) =1.56; 95% confidence interval (95%CI) 1.11-2.18) and (HR=1.31; 95%CI 1.05-1.63), but not among males with high leisure time physical activity (HR=1.00; 95%CI 0.78-1.26) (test for interaction $p=0.04$). Similar, but weaker tendencies were found for myocardial infarction. Among women, occupational physical activity was not associated with subsequent all-cause mortality or MI.

Conclusions The findings suggest that high occupational physical activity imposes harmful effects particularly among men with low levels of leisure time physical activity.

ARTICLE SUMMARY

Article focus

- Men with low physical fitness and high occupational physical activity are recently shown to have an increased risk of cardiovascular disease and all-cause mortality.
- It is unknown if the association between occupational physical activity with cardiovascular disease and all-cause mortality also depends on leisure time physical activity.

Key messages

- This study shows that men with high occupational physical activity have an increased risk of all-cause mortality.
- Leisure time physical activity was found to modify the positive association between occupational physical activity and risk of all-cause mortality. High occupational physical activity imposes harmful effects particularly among men with low levels of leisure time physical activity.

Strengths and limitations

Study strengths include the long follow-up time, repeated assessment of the occupational physical activity, objective measures of several covariates from clinical examinations, and information on outcomes obtained from valid registers, and participation of both sexes. Some limitations are the lack of control for psychosocial work factors and the self-reported exposures.

INTRODUCTION

A positive association has been demonstrated between occupational physical activity and risk of cardiovascular and all-cause mortality among men with low cardiorespiratory capacity, i.e. physical fitness [1]. A physiological explanation may be prolonged intravascular turbulence and increased wall shear stress from occupational physical activity several hours per day [2], inducing inflammatory processes in the arterial walls eventually leading to atherosclerosis [3].

Theoretically, these acute adverse effects of occupational physical activity may be modified by leisure time physical activity known to promote cardio-respiratory fitness [4] and reduce heart rate and blood pressure during daily activities [5]. A higher cardio-respiratory fitness and lower heart rate provides a longer period in the diastolic phase of the cardiac cycle, causing better myocardium perfusion and reduced intravascular turbulence and wall shear stress, lowering the risk of inflammation and atherosclerosis [2, 3]. Therefore, the increased cardio-respiratory fitness and reduced heart rate and blood pressure from leisure time physical activity may counteract the prolonged intravascular turbulence and increased wall shear stress from occupational physical activity. We have previously shown that high occupational physical activity confers an increased risk of cardiovascular and all-cause mortality among men with a low physical fitness, but not among men with high physical fitness [1]. However, the role of leisure time physical activity on the risk for cardiovascular disease and mortality from high occupational physical activity remains unsettled.

Relatively few studies have investigated the effects of occupational physical activity on cardiovascular disease and mortality among females [6]. Because type of occupational physical activity differs between male and female occupations [7] the effects of occupational physical activity on cardiovascular health may depend on sex. A recent editorial on occupational physical activity and cardiovascular health highlights the need for future investigations in additional cohorts among both sexes [8].

Accordingly, we hypothesized that high occupational physical activity is an independent risk factor for myocardial infarction and all-cause mortality in both men and women. Finally, we hypothesized that the level of leisure time physical activity in both sexes modifies the association between occupational physical activity and risk of myocardial infarction and all-cause mortality.

MATERIALS AND METHODS

Study population

The Copenhagen City Heart Study is a prospective cardiovascular population study comprising a random sample of 19,698 males and females aged 20 to 101 years, drawn from the Copenhagen Population Register as of January 1, 1976. The first survey lasted from 1976 to 1978 (response rate 74%) and the second from 1981 to 1983 (response rate 70%). A total of 11,135 persons participated in both examinations.

Participants with previous myocardial infarction or stroke by self-report or according to the Danish National Patient Register established in 1977 were excluded (n= 644). Moreover, all persons above the age of retirement in Denmark at the time of the second examination (i.e. 67 years of age) were excluded, leaving 8,496 persons eligible. Finally, we excluded the 677 persons with missing values in occupational physical activity in one of the surveys, leaving 7,819 eligible for analyses.

Established cardiovascular risk factors were assessed at both examinations using a self-administered questionnaire and a physical examination. The Ethics Committee for the Copenhagen area approved the study (KF 100.2039/91).

Occupational physical activity (the main predictor variable)

A single question with four categories was applied for measuring occupational physical activity:

‘Which description most precisely covers your pattern of physical activity at work? [9]

1. You are mainly sedentary and do not walk much around at your workplace. *E.g.* desk work, work including assembling of minor parts. [Score 1]
2. You walk around quite a bit at your workplace but do not have to carry heavy items. *E.g.* light industrial work, non-sedentary office work, inspection and the like. [Score 2]
3. Most of the time you walk, and you often have to walk up stairs and lift various items. Examples include mail delivery and construction work. [Score 3]
4. You have heavy physical work. You carry heavy burdens and carry out physically strenuous work. *E.g.* work including digging and shoveling. [Score 4]

To reduce risk of misclassification, the main predictor variable was based on combined information from assessment in 1976-78 and 1981-83, summarizing the total sum of scores. Then, the scores were categorized into: “low” = score 2-3, “moderate” = score 4-5, and “high” = score 6-8.

Leisure time physical activity (the potential effect modifier)

A single question with four categories was applied for measuring leisure time physical activity:

‘Which description most precisely covers your pattern of physical activity during leisure time? [10]

1. Being almost entirely sedentary (e.g., reading, watching television or movies, engaging in light physical activity such as walking or biking for less than 2 hours per week). [Score 1]
2. Engaging in light physical activity for 2–4 hours per week. [Score 2]
3. Engaging in light physical activity for more than 4 hours per week or more vigorous activity for 2–4 hours per week (e.g., brisk walking, fast biking, heavy gardening, sports that cause perspiration or exhaustion). [Score 3]
4. Engaging in highly vigorous physical activity for more than 4 hours per week or regular heavy exercise or competitive sports several times per week. [Score 4]’

Because of very few females (n=52) and males (n=140) in the highest category of leisure time physical activity, the variable was categorised into: score 1 = “low”, score 2 = “moderate”, and score 3-4 = “high”.

Potential confounders

Potentially confounding factors for the association between occupational physical activity and cardiovascular health and mortality were measured as follows: smoking habits were categorized into never smokers, ex-smokers, and current smokers of <15, ≥15 g of tobacco per day. Current tobacco consumption was calculated by equating a cigarette to 1 g of tobacco, a cheroot to 3 g of tobacco, and a cigar to 5 g of tobacco. Systolic blood pressure was measured in a sitting position after 5 minutes of rest. Diabetes and use of anti-hypertensive medication were self-reported. Those reporting to use anti-hypertensive medication were defined as hypertensive. Body mass index (BMI) was calculated as measured weight (kg) divided by height squared (m²). Alcohol consumption was categorized as abstention, monthly, weekly, or daily intake of at least 1 unit of alcohol. Household income was self-reported based on average income per month within the last year, and stratified into low, medium and high. Cholesterol was measured non-fasting in mmol/L. Details of the potential confounders are previously published [11].

Follow-up

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4 Subjects were followed in national registers from the second examination (1981-83) until December
5 2008 for myocardial infarction and May 2010 for all-cause mortality. The end-point myocardial
6 infarction was defined as the first incidence of fatal or non-fatal myocardial infarction according to
7 the International Classification of Diseases: 8th revision code 410, and 10th revision codes I21–I22.
8 Episodes of non-fatal myocardial infarction were retrieved from The National Hospital Discharge
9 Register. Deaths were obtained from The Civil Registration System and causes of death from The
10 National Register of Causes of Death. To reduce the maximum follow-up time without exposure to
11 occupational physical activity to 10 years (the pension age is 67 years in Denmark), persons were
12 censored from follow-up analyses at 77 years of age. Subjects were thus followed until outcome,
13 age 77 or end of follow-up in 2010, whatever came first. The median duration of follow-up was
14 17.8 years (range 0 - 27.7) for myocardial infarction and 18.4 years (range 0 - 29.4) for all-cause
15 mortality.
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24 25 26 **Analyses**

27 For demographics, Pearson's chi-square test was used for categorical covariates and one-way
28 ANOVA for continuous covariates.
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32 The associations between occupational physical activity and fatal and non-fatal myocardial
33 infarction, and all-cause mortality were studied using sex-specific Cox proportional hazards
34 regression models. Associations were investigated both overall and stratified according to level of
35 leisure time physical activity. The Cox models were performed with age as underlying time scale
36 and age at baseline as entry time. All adjusted models included the covariates smoking, alcohol
37 consumption, BMI, leisure time physical activity, systolic blood pressure, diabetes, blood pressure
38 medication, cholesterol and household income. We tested for interaction between sex, occupational
39 physical activity, and the outcomes all-cause mortality and myocardial infarction. Deviation from
40 the proportional hazards assumption was evaluated by Schoenfeld residuals, and by inspection of
41 log-log plots. P-values below 0.05 were considered statistically significant. Statistical analyses were
42 performed with R version 2.13.1.
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52 Moreover, we tested for interaction between occupational physical activity, leisure time physical
53 activity, and the outcomes all-cause mortality and myocardial infarction.
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Two additional analyses were performed. In the first analysis, the risk of all-cause mortality and myocardial infarction was investigated including exclusively males and females who had not changed their level of occupational physical activity from the first (1976-78) to the second examination (1981-83). Due to the low number of females in the highest category of occupational physical activity (n=2), the variable was categorized as: “low” = score 1, “moderate” = score 2, and “high” = scores 3 and 4 pooled. Because of the strong association between occupational physical activity and years of education, we found it necessary to carry out a second additional analysis including only those with a maximum school length of 10 years.

RESULTS

A total of 1,493 (41.4%) males and 1,395 (28.5%) females died; 511 (14.2%) males and 276 (5.6%) females experienced a first myocardial infarction episode during the follow-up period.

Table 1 shows lifestyle and other characteristics according to level of occupational physical activity among males and females. Several significant differences were found, but differences were generally small with no clear positive or negative trends. However, men with high occupational physical activity were more frequently smokers, had higher BMI, fewer with hypertension, and fewer with long (>10 years) school education. Among females, women with high occupational physical activity had lower alcohol consumption, a lower leisure time physical activity level, lower systolic blood pressure, and fewer had a long school education.

Table 2 shows the distribution of participants in the four groups of occupational physical activity among males and females without a history of cardiovascular disease at the first examination (1976-78) and the second examination (1981-83) in the Copenhagen City Heart Study. Level of occupational physical activity remained constant between the two examinations for 61.0%, decreased for 22.6% and increased for 16.4% of the participants.

Table 3 shows the association between occupational physical activity and risk of all-cause mortality and myocardial infarction stratified by sex. The occupational physical activity variable consisted of the combined measure of occupational physical activity in 1976-78 and 1981-83. Among males, the risk of myocardial infarction increased with higher occupational physical activity but only significantly among men with moderate exposure. For all-cause mortality, occupational physical

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4 activity increased the risk in a dose-response manner (test for trend, $p=0.008$). Males with moderate
5 occupational physical activity had an increased risk of 15% while those with high occupational
6 physical activity had a 22% increase in all-cause mortality referencing males with low occupational
7 physical activity. Among females, no tendency was found that increasing occupational physical
8 activity increased the risk of either all-cause mortality or myocardial infarction.
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14 The association between occupational physical activity and both outcomes differed by sex even
15 after control for potential confounders, test for interaction being significant ($p=0.02$) for both all-
16 cause mortality and myocardial infarction.
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21 In the additional analysis comprising only participants with unchanged level of occupational
22 physical activity from the first (1976-78) to the second examination (1981-83), i.e. those shown in
23 bold in Table 2 ($n=4,766$), the risk estimates did not differ materially from the original model
24 including all participants (data not shown).
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29 Table 4 shows the association between the combined measure of occupational physical activity and
30 risk of all-cause mortality and myocardial infarction stratified by leisure time physical activity
31 among males and females. Among men with low or moderate leisure time physical activity, risk of
32 all-cause mortality was increased with higher occupational physical activity (test for trend, $p=0.01$
33 in both cases). However, among men who were highly physically active during leisure time, the risk
34 of all-cause mortality was independent of occupational physical activity level. A significant
35 interaction between occupational and leisure time physical activity was found ($p=0.04$) even after
36 control for potential confounders. Similar tendencies, although non-significant, were found for
37 myocardial infarction among males. Among females, occupational physical activity did not increase
38 either the risk of all-cause mortality or myocardial infarction in any of the leisure time physical
39 activity groups and no significant interaction was found.
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49 In the additional analysis including only those with a maximum school length of 10 years, the
50 multi-adjusted analyses among males showed a significant increased risk of all-cause mortality
51 from moderate ($HR=1.17$; $95\%CI=1.00-1.37$) and high ($HR=1.21$; $95\%CI=1.03-1.42$) occupational
52 physical activity, but no significantly increased risk for myocardial infarction from moderate
53 ($HR=1.27$; $95\%CI=0.98-1.65$) and high ($HR=1.11$; $95\%CI=0.85-1.46$) occupational physical
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4 activity. Among females with a maximum school length of 10 years, occupational physical activity
5 was not significantly associated with all-cause mortality or myocardial infarction.
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9 **COMMENTS**

10 The primary finding of this study was the observation that leisure time physical activity modifies
11 the positive association between occupational physical activity and risk of all-cause mortality. The
12 second observation relating to the aim of the present study was the clear difference between males
13 and females regarding occupational physical activity as a predictor of all-cause mortality and
14 myocardial infarction. Overall, occupational physical activity did not predict risk among women.
15 The third finding was that, overall, among men with a high occupational physical activity a
16 statistically significant increased risk of all-cause mortality was seen, also when controlling for
17 relevant confounders. Regarding myocardial infarction risk, the results were less clear but with
18 similar tendencies.
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27 The observations of the present study are in agreement with a number of previous studies
28 addressing the association between high occupational physical activity and increased risk of all-
29 cause mortality and cardiovascular disease [3, 6, 12-14]. The observation of a modifying effect of
30 leisure time physical activity is in agreement with our previous observation that a high physical
31 fitness seemed to completely counteract the positive association between occupational physical
32 activity and risk of all-cause mortality and even ischaemic heart disease mortality [1].
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39 Physical activity is regarded as beneficial for cardiovascular health but a distinction should be made
40 between leisure time and occupational physical activity [14]. In contrast to leisure time physical
41 activity, most occupational physical activity in modern industrialized societies does not include
42 activities with high enough intensity to increase the maximal oxygen uptake capacity (physical
43 fitness) [1]. Such activities encompass regular dynamic use of large muscle groups with high
44 intensity and sufficient time for recovery [15, 16]. An explanation for the increased risk of mortality
45 attributed to high occupational physical activity may include hemodynamic effects on the
46 cardiovascular system promoting the development of atherosclerosis [2]. Several hours per day of
47 high levels of occupational physical activity will inevitably cause prolonged elevated heart rate,
48 eliciting a higher fraction of the cardiac cycle in the systolic phase with unfavorable intravascular
49 turbulence and wall shear stress, leading to inflammatory processes in the arterial walls, which may
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4 result in atherosclerosis, cardiovascular disease and death [3]. Because of the distinctive effect of
5 leisure time and occupational physical activity, non-specified (total) measurements of physical
6 activity are likely to provide attenuated cardiovascular risk estimates. Therefore, measurements of
7 physical activity ought to be domain specific.
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12 As illustrated in table 2, most study participants did not change their level of occupational physical
13 activity from the first examination (1976-78) to the second examination (1981-83). Among the 39%
14 who did, changes were typically small and mostly to lower levels of occupational physical activity.
15 Additional analyses on the association between occupational physical activity and all-cause
16 mortality and myocardial infarction exclusively including participants who reported the same level
17 of occupational physical activity at both examinations, showed results that were practically identical
18 with the analyses based on the entire study population (data not shown). So, it seems unlikely that
19 the observed positive association between occupational physical activity and all-cause mortality as
20 well as myocardial infarction can be attributed to occupational physical activity changes due to
21 health problems. Moreover, the significantly increased multi-adjusted risk of all-cause mortality
22 from high occupational physical activity among males with a low educational level (<10 years)
23 indicates that the observed association between occupational physical activity and all-cause
24 mortality not is a result of socioeconomic confounding.
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36 In contrast to the significant relationship among men, occupational physical activity was not a
37 predictor of either all-cause mortality or myocardial infarction among women. The most likely
38 reason for this difference is the fact that occupational physical activity qualitatively and
39 quantitatively may reflect different physiological impacts from male and female works tasks,
40 respectively. Lifting of heavy burdens, i.e. isometric work is a much more frequent work task in
41 male occupations, and more dynamic work tasks more frequently characterize manual female work
42 demands [7]. It is well known that heavy isometric work induces an acute rise in blood pressure
43 with a subsequent induction of arterial wall shear stress. Due to the more dynamic occupational
44 work tasks for females, this physiological effect may not be nearly as pronounced as for males.
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51 52 *Strengths and limitations*

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54 The main strengths of the present study include the prospective design, the large size of a random
55 sample of both men and women representative of the population of Copenhagen, long follow-up
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4 time, almost 100% follow-up on national registers, repeated assessment of the occupational physical
5 activity, objective measures of several covariates from clinical examinations, and information on
6 outcomes obtained from valid registers, and participation of both sex. Some limitations of the study
7 should be addressed: 1) the lack of control for psychosocial work factors, 2) exposures are self-
8 reported, 3) the leisure time physical activity was only measured at baseline. Ad 1) Previous studies
9 have shown that control for psychosocial work factors have minimal influence on the association
10 between occupational physical activity and cardiovascular disease and mortality [3, 6]. It is
11 unknown if a potential bias due to lack of control for psychosocial work factors would increase or
12 attenuate the risk estimates. Ad 2) Another limitation of the present study is that the occupational
13 physical activity and leisure time physical activity information was based on self-assessment, which
14 may entail some degree of misclassification [17]. Such misclassification would however not explain
15 the findings presented, as the potential bias would rather attenuate the risk estimates.

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17 Moreover, the rather crude measure of alcohol consumption may have caused some
18 misclassification of alcohol consumption. Because of the very few participants responding in the
19 highest category of leisure time physical activity, the highest category was merged with the second
20 highest category of leisure time physical activity. However, merging of the responses to these
21 categories could only have a minor impact on the risk estimates from the second highest category
22 alone. Although the occupational physical activity was measured at different ages in this study
23 population with a large age range (25-66 years), the rather similar mean age in the groups with
24 different levels of occupational physical activity (table 1) makes it unlikely that this would
25 influence the results of the study.

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In conclusion, occupational physical activity was a predictor of all-cause mortality as well as
myocardial infarction in men, but not in women. Occupational physical activity was positively
associated with risk of all-cause mortality in males with low and moderate leisure time physical
activity, but not in males with high leisure time physical activity. The results suggest that high
occupational physical activity imposes harmful effects particular among men with lower levels of
leisure time physical activity. Sex differences in the relationship between occupational physical
activity and risk of all-cause mortality and myocardial infarction may reflect qualitative as well as
quantitative differences with respect to occupational physical exposures.

TABLES

Table 1. Demographic and lifestyle factors of males and females between 20 and 67 years of age without a history of cardiovascular disorders stratified by level of occupational physical activity from the second examination (1981-83) in the Copenhagen City Heart Study, n=7,819. P-values of differences between the groups of occupational physical activity are provided.

Sex:	Males				Females			
	Occupational physical activity	Low n = 1,114	Moderate n = 1,152	High n = 1,015	p- value	Low n = 1,506	Moderate n = 2,303	High n = 729
Age, mean (SD)	52.1 (10.2)	53.0 (9.4)	51.5 (8.6)	<0.001	54.1 (9.1)	54.4 (9.0)	49.7 (9.1)	<0.001
BMI, mean (SD)	25.6 (3.9)	26.0 (3.7)	26.6 (3.7)	<0.001	24.5 (4.3)	24.9 (4.6)	24.8 (4.3)	0.04
Current smokers, %	62.9	65.7	69.1	<0.01	55.6	54.0	59.8	0.02
Consuming ≥ 1 unit alcohol a day, %	34.8	32.9	41.5	<0.001	13.4	10.8	7.1	<0.001
Low leisure time physical activity, %	14.9	11.8	14.3	<0.001	16.5	13.4	11.0	<0.001
Systolic blood pressure, mean (SD)	140.4 (19.4)	140.9 (19.5)	139.1 (18.8)	0.08	135.2 (20.9)	136.8 (20.6)	131.1 (19.6)	<0.001
Blood pressure medication, %	8.7	7.6	5.4	0.01	9.6	9.2	7.1	0.15
Diabetes, %	4.0	3.7	3.7	0.91	1.5	1.7	1.0	0.36
Low income, %	9.3	12.2	9.0	<0.001	18.5	27.7	17.2	<0.001
High school education (>10 years), %	37.3	17.1	3.8	<0.001	20.6	12.8	10.8	<0.001
Cholesterol, mmol/L	5.7 (1.1)	5.8 (1.1)	5.8 (1.1)	0.40	6.0 (1.2)	6.0 (1.2)	5.8 (1.2)	<0.001

Table 2. Distribution of participants in the four levels of occupational physical activity among males and females between 20 and 67 years of age without a history of cardiovascular disorders at the first examination (1976-78) and the second examination (1981-83) in the Copenhagen City Heart Study, n=7,819. Numbers in bold are those males and females who did not change their level of occupational physical activity from the first (1976-78) to the second examination (1981-83).

Sex	physical	Males				Females			
		Low (1981- 83)	Moderate (1981- 83)	High (1981- 83)	Very high (1981-83)	Low (1981- 83)	Moderate (1981- 83)	High (1981- 83)	Very high (1981-83)
Occupational									
activity									
Low (1976-78)		698	188	51	7	797	347	62	0
Moderate (1976-78)		228	536	191	13	362	1,304	352	2
High (1976-78)		108	201	513	64	117	468	704	5
Very high (1976-78)		58	67	146	212	0	5	11	2

Table 3. Combined measure of occupational physical activity from 1976-78 and 1981-83 as predictor for fatal and non-fatal myocardial infarction and all-cause mortality among males and females between 20 and 67 years of age without a history of cardiovascular disorders in the Copenhagen City Heart Study (n=7,819).

		Person- years	No. of cases (%)	Hazard Ratio (95% CI) ^a	Hazard Ratio (95% CI) ^b
Males					
<i>Myocardial infarction</i>					
Occupational physical activity					
Low	(n=1,114)	19,941	133 (12%)	1 (reference)	1 (reference)
Moderate	(n=1,152)	19,828	183 (16%)	1.34 (1.07-1.68)**	1.30 (1.03-1.64)*
High	(n=1,015)	18,424	145 (14%)	1.18 (0.93-1.50)	1.20 (0.93-1.55)
<i>All-cause mortality</i>					
Occupational physical activity					
Low	(n=1,114)	21,108	395 (35%)	1 (reference)	1 (reference)
Moderate	(n=1,152)	21,136	478 (41%)	1.17 (1.02-1.33)*	1.15 (1.01-1.33)*
High	(n=1,015)	19,596	435 (43%)	1.21 (1.05-1.38)**	1.22 (1.05-1.41)**
Females					
<i>Myocardial infarction</i>					
Occupational physical activity					
Low	(n=1,506)	27,403	87 (6%)	1 (reference)	1 (reference)
Moderate	(n=2,303)	41,944	113 (5%)	0.82 (0.62-1.09)	0.76 (0.56-1.02)
High	(n=729)	15,257	45 (6%)	1.10 (0.76-1.57)	0.98 (0.67-1.44)
<i>All-cause mortality</i>					
Occupational physical activity					
Low	(n=1,506)	28,326	439 (29%)	1 (reference)	1 (reference)
Moderate	(n=2,303)	43,330	619 (27%)	0.89 (0.79-1.01)	0.88 (0.78-1.00)
High	(n=729)	15,901	194 (27%)	0.96 (0.81-1.14)	0.95 (0.79-1.13)

^a: Control made for age

^b: Control made for age, smoking, alcohol, BMI, leisure time physical activity, systolic blood pressure, diabetes, cholesterol, blood pressure medication, and household income

*: $p \leq 0.05$, **: $p \leq 0.01$

Table 4. Combined measure of occupational physical activity from 1976-78 and 1981-83 as predictor for fatal and non-fatal myocardial infarction and all-cause mortality among males and females between 20 and 67 years of age without a history of cardiovascular disorders stratified on leisure time physical activity in 1981-83 in the Copenhagen City Heart Study (n=7,816).

	Occupational physical activity	Person-years	No. of cases (%)	Hazard Ratio (95% CI)^a	Hazard Ratio (95% CI)^b
Males					
<i>Myocardial infarction</i>					
Low leisure time physical activity (n=447)	Low (n=166)	2,825	25 (15%)	1 (reference)	1 (reference)
	Moderate (n=136)	2,248	25 (18%)	1.28 (0.74-2.23)	1.39 (0.76-2.53)
	High (n=145)	2,382	23 (16%)	1.15 (0.65-2.03)	1.15 (0.62-2.13)
Moderate leisure time physical activity (n=1,468)	Low (n=531)	9,544	59 (11%)	1 (reference)	1 (reference)
	Moderate (n=532)	9,131	82 (15%)	1.39 (1.00-1.95)	1.27 (0.89-1.80)
	High (n=405)	7,254	63 (16%)	1.43 (1.00-2.04)*	1.41 (0.96-2.06)
High leisure time physical activity (n=1,364)	Low (n=417)	7,572	49 (12%)	1 (reference)	1 (reference)
	Moderate (n=483)	8,442	75 (16%)	1.31 (0.92-1.88)	1.27 (0.87-1.86)
	High (n=464)	8,761	59 (13%)	1.00 (0.69-1.47)	1.04 (0.69-1.55)
<i>All-cause mortality</i>					
Low leisure time physical activity (n=447)	Low (n=166)	3,012	74 (45%)	1 (reference)	1 (reference)
	Moderate (n=136)	2,422	73 (54%)	1.27 (0.92-1.75)	1.15 (0.81-1.62)
	High (n=145)	2,549	85 (59%)	1.48 (1.08-2.02)*	1.56 (1.11-2.18)*
Moderate leisure time physical activity (n=1,468)	Low (n=531)	10,049	185 (35%)	1 (reference)	1 (reference)
	Moderate (n=532)	9,702	230 (43%)	1.24 (1.02-1.50)*	1.28 (1.05-1.57)*
	High (n=405)	7,794	179 (44%)	1.29 (1.05-1.59)*	1.31 (1.05-1.63)*
High leisure time physical activity (n=1,364)	Low (n=417)	8,048	136 (33%)	1 (reference)	1 (reference)
	Moderate (n=483)	8,997	174 (36%)	1.08 (0.86-1.35)	0.96 (0.76-1.22)
	High (n=464)	9,226	171 (37%)	1.06 (0.85-1.33)	1.00 (0.78-1.26)
Females					
<i>Myocardial infarction</i>					
Low leisure time physical activity (n=637)	Low (n=248)	4,085	17 (7%)	1 (reference)	1 (reference)
	Moderate (n=309)	5,335	18 (6%)	0.82 (0.42-1.59)	1.03 (0.49-2.15)
	High (n=80)	1,564	7 (9%)	1.13 (0.47-2.73)	1.55 (0.55-4.35)
Moderate leisure time physical activity (n=2,568)	Low (n=899)	16,632	58 (6%)	1 (reference)	1 (reference)
	Moderate (n=1,317)	24,387	63 (5%)	0.72 (0.50-1.03)	0.65 (0.45-0.95)*
	High (n=352)	7,427	22 (6%)	1.01 (0.62-1.65)	0.78 (0.46-1.33)
High leisure time physical activity (n=1,332)	Low (n=358)	6,671	12 (3%)	1 (reference)	1 (reference)
	Moderate (n=677)	12,222	32 (5%)	1.38 (0.71-2.68)	1.00 (0.49-2.01)
	High (n=297)	6,266	16 (5%)	1.75 (0.82-3.70)	1.18 (0.54-2.60)
<i>All-cause mortality</i>					
Low leisure time physical activity (n=637)	Low (n=248)	4,247	94 (38%)	1 (reference)	1 (reference)
	Moderate (n=309)	5,503	106 (34%)	0.87 (0.66-1.14)	0.89 (0.66-1.20)
	High (n=80)	1,612	30 (38%)	0.91 (0.60-1.37)	0.99 (0.63-1.54)
Moderate leisure time physical activity (n=2,568)	Low (n=899)	17,210	259 (29%)	1 (reference)	1 (reference)
	Moderate (n=1,317)	25,221	325 (25%)	0.83 (0.70-0.98)*	0.80 (0.68-0.95)*
	High (n=352)	7,726	90 (26%)	0.93 (0.73-1.18)	0.92 (0.71-1.18)
High leisure time physical activity (n=1,332)	Low (n=358)	6,853	86 (24%)	1 (reference)	1 (reference)
	Moderate (n=677)	12,607	188 (28%)	1.12 (0.87-1.45)	1.06 (0.81-1.39)
	High (n=297)	6,563	74 (25%)	1.18 (0.86-1.61)	1.05 (0.76-1.45)

^a: Control made for age

^b: Control made for age, smoking, alcohol, BMI, systolic blood pressure, diabetes, cholesterol, blood pressure medication, and household income

*: $p \leq 0.05$, **: $p \leq 0.01$

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42
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45

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48 All authors contributed to the conception, design, interpretation of data, and writing or critically
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51

52 **ETHICAL APPROVAL**

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54 The Ethics Committee for the Copenhagen area Denmark approved the study (KF 100.2039/91).
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

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