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The physical activity paradox in cardiovascular disease and all-cause mortality: the contemporary Copenhagen General Population Study with 104 046 adults

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Aims Leisure time physical activity associates with reduced risk of cardiovascular disease and all-cause mortality, while these relationships for occupational physical activity are unclear. We tested the hypothesis that leisure time physical activity associates with reduced major adverse cardiovascular events (MACE) and all-cause mortality risk, while occupational physical activity associates with increased risks.

Methods and results We studied 104 046 women and men aged 20–100 years in the Copenhagen General Population Study with baseline measurements in 2003–2014 and median 10-year follow-up. Both leisure and occupational physical activity were based on self-report with four response categories. We observed 7913 (7.6%) MACE and 9846 (9.5%) deaths from all causes. Compared to low leisure time physical activity, multivariable adjusted (for lifestyle, health, living conditions, and socioeconomic factors) hazard ratios for MACE were 0.86 (0.78–0.96) for moderate, 0.77 (0.69–0.86) for high, and 0.85 (0.73–0.98) for very high activity; corresponding values for higher occupational physical activity were 1.04 (0.95–1.14), 1.15 (1.04–1.28), and 1.35 (1.14–1.59), respectively. For all-cause mortality, corresponding hazard ratios for higher leisure time physical activity were 0.74 (0.68–0.81), 0.59 (0.54–0.64), and 0.60 (0.52–0.69), and for higher occupational physical activity 1.06 (0.96–1.16), 1.13 (1.01–1.27), and 1.27 (1.05–1.54), respectively. Similar results were found within strata on lifestyle, health, living conditions, and socioeconomic factors, and when excluding individuals dying within the first 5 years of follow-up. Levels of the two domains of physical activity did not interact on risk of MACE ($P = 0.40$) or all-cause mortality ($P = 0.31$).

Conclusion Higher leisure time physical activity associates with reduced MACE and all-cause mortality risk, while higher occupational physical activity associates with increased risks, independent of each other.

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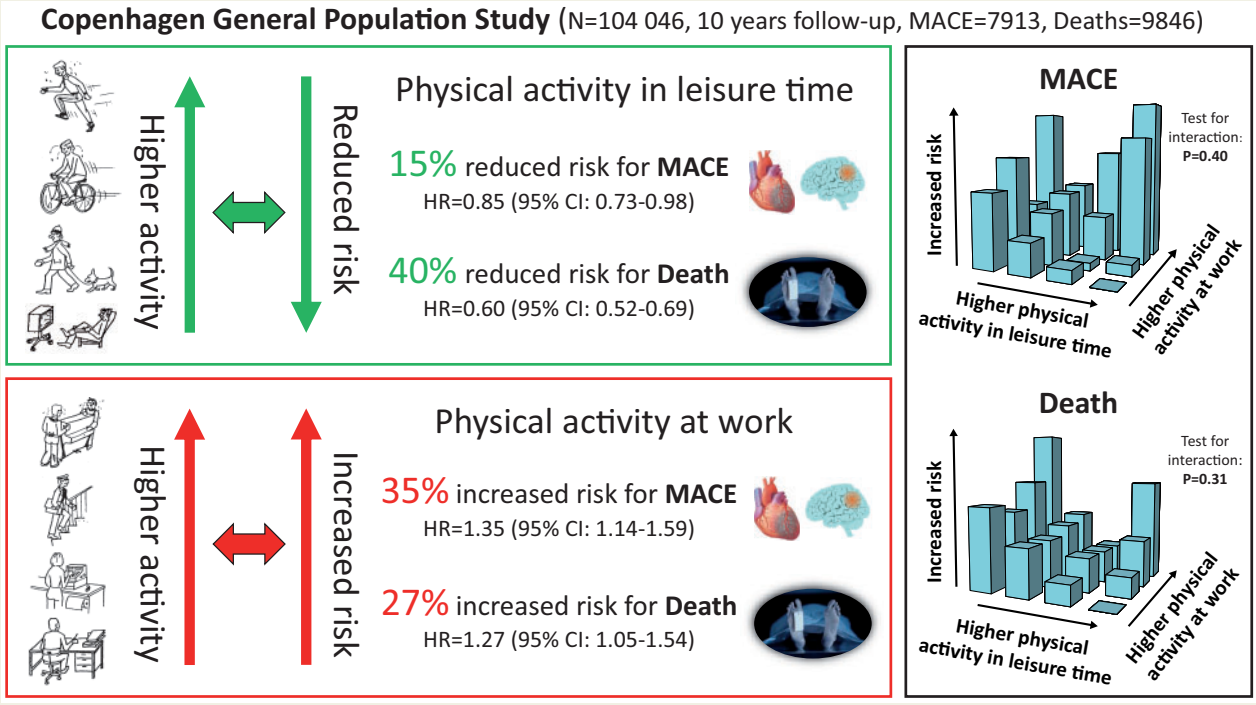
Graphical Abstract



Risk of major adverse cardiovascular events (MACE) and all-cause mortality as a function of different categories of leisure time physical activity and occupational physical activity in individuals in the Copenhagen General Population Study.

Keywords Physical activity • Stroke • Cardiovascular disease • Occupational health • Morbidity • Mortality

Introduction

Physical activity is a strong preventive measure of cardiovascular disease and all-cause mortality.[1,2] However, recent studies have observed that the potential health effect of physical activity depends on the domain in which it is performed.[3–5] While leisure time physical activity (e.g. sports, recreation, and transportation) is well documented to be beneficially associated with cardiovascular disease and all-cause mortality,[1,2,6] then occupational physical activity is not consistently reported to associate with improved health.[7–10] A systematic review even found that men with high vs. low occupational physical activity had increased risk of all-cause mortality.[11] A recent umbrella review found that high occupational physical activity is associated with reduced risk of some health outcomes (i.e. cancers, coronary heart disease, and type 2 diabetes), but with increased risk of other health outcomes (i.e. osteoarthritis, poor sleep quality, and all-cause mortality in men).[12] The authors concluded that 'there is a need for better quality evidence to provide a unequivocal statement on the health effects of occupational physical activity'.[12]

This potential contrasting health effect of leisure time physical activity and occupational physical activity is termed the 'physical activity paradox'.[13] An explanation for the physical activity paradox likely is the very different characteristics of physical activity when performed during leisure time and work.[14] Leisure time physical activity often includes dynamic movements at conditioning intensity levels sufficient to improve cardiorespiratory fitness over short time periods with enough recovery time.[14] In contrast, work often requires static loading, monotonous and awkward working postures, and other non-conditioning activities over several hours per day without sufficient recovery time.[14]

However, recent physical activity guidelines do not differentiate between work and leisure time domains.[1,2] Work constitutes the main domain for physical activity for a large fraction of the adult population worldwide.[15,16] We are not aware of any international or national physical activity guidelines differentiating on occupational physical activity and leisure time physical activity. If the physical activity paradox holds true, this can contribute to the understanding and interventions on the generally poor health of individuals with high occupational physical activity.

We hypothesized that leisure time physical activity associates with reduced cardiovascular disease and all-cause mortality while occupational physical activity associates with increased risks. To do so, we investigated the risk of major adverse cardiovascular events (MACE) and death from all causes in relation to occupational physical activity and leisure time physical activity in the large contemporary Copenhagen General Population Study with baseline measurements in

2003–2014. To minimize risk for confounding and reverse causation, we performed multivariable adjusted analyses including extensive adjustments for potential lifestyle, health, living conditions, and socioeconomic confounders, as well as in strata of potential confounders, and when excluding individuals dying within the first 5 years of follow-up.

Methods

The Copenhagen General Population Study was established in 2003–2014. Women and men aged 20–100 years were randomly invited from the general population of the greater Copenhagen area including both high- and low-income areas, using the Danish Central Person Registration number, which uniquely identifies all individuals living in Denmark. All individuals were Whites and of Danish descent. The study was approved by a Danish ethics committee (H-KF-01-144/01) and by Herlev Gentofte Hospital, Copenhagen University Hospital. The study was conducted according to the Declaration of Helsinki, and all participants gave written informed consent. Of the 256 761 individuals invited, 43% participated. In Supplementary material online, *Figure S1*, we show MACE and all-cause mortality as a function of follow-up time for responders and non-responders separately.

Covariates

The participants filled out a questionnaire and underwent a physical health examination including measurements of height, weight [from which body mass index (BMI) was calculated as kg/m^2] and resting blood pressure and heart rate. From the questionnaire, information was obtained about leisure time physical activity, occupational physical activity, educational background [categorized as below middle school (<8 years), middle school (8–10 years), high school (>10 years), and university], living conditions and socioeconomic status (household income, longest employment since school, cohabitation, marital status), smoking (categorized as never smoker, former smoker, and current smoking), alcohol consumption (reported drinks per week), adherence to dietary guidelines,[17] blood pressure medication, and a vital exhaustion score. Diabetes was based on self-report or a non-fasting blood glucose ≥11.1 mmol/L (200 mg/dL). Information on previous cardiovascular disease was based on register data. Standard hospital assays measured low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, plasma triglycerides, and plasma glucose on non-fasting blood samples drawn at study examination. Chronic obstructive pulmonary disease (COPD) according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages 1–4 was based on baseline spirometry. The Danish Central Person Registration number provides data on age and sex.

Exposures

Occupational physical activity was quantitated using the following question used in numerous previous studies[18]: 'What is your physical activity at work within the last year?'

(1) Predominantly sedentary work.
(2) Sedentary or standing, sometimes walking work.
(3) Walking, sometimes lifting work.
(4) Heavy manual work.

Leisure time physical activity was quantitated by the following question used in numerous previous studies[18]: 'What is your physical activity during leisure time (including transport to and from work) within the last year?'

(1) Almost completely sedentary or light physical activity less than 2 hours per week.
(2) Light physical activity for 2–4 hours per week.
(3) Light physical activity for more than 4 hours per week or vigorous physical activity for 2–4 hours per week.
(4) Vigorous physical activity for more than 4 hours per week or regular heavy exercise or competitive sports several times per week.

Outcomes

The follow-up on outcomes started the day after the baseline measurements. MACE consisted of fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, and other coronary death. Individuals with pre-existing MACE (n = 5282) were excluded from the statistical analyses to avoid reverse causality.

These outcomes were identified by linkage to the national Danish Patient Registry covering all Danish hospitals and to the national Danish Cause of Death Registry, using the following ICD-10 codes: I21 and I22 for non-fatal MI and I20-I25 for fatal coronary heart disease. Possible stroke events (among hospitalized patients) were identified with the ICD-10 codes I60, I61, I63, I64, and G45 and subsequently validated using the World Health Organization definition of stroke, that is an acute disturbance of focal or global cerebral function with symptoms lasting longer than 24 h or leading to death, with presumably no other reasons than of vascular origin.[19]

Deaths were obtained until December 2018 from the Civil Registration System and causes of death until December 2016 from the Danish Register of Causes of Death. The median follow-up time was 9.5 years (Q1–Q3: 6.8–11.9; maximum: 15.0) for cardiovascular events and 9.9 years (Q1–Q3: 7.1–12.3; maximum: 15.0 years) for all-cause mortality.

Statistical analyses

The median follow-up time was based on the reverse Kaplan–Meier method.[20] The associations between predictors (i.e. leisure time physical activity and occupational physical activity) and all-cause mortality were studied using Cox proportional hazards regression analysis and cause-specific Cox proportional hazards regression analysis for MACE, where deaths from other causes were considered a competing risk. All models had follow-up time as underlying time scale. Adjustments were done in three steps: model A, age and sex; a multivariable adjusted model B, model A + BMI, smoking, years in school, diabetes, systolic blood pressure, blood pressure medication, dietary preferences, alcohol consumption, COPD by GOLD stage, LDL cholesterol, HDL cholesterol, and triglycerides; and an extended multivariable sensitivity model C, model B + resting heart rate, vital exhaustion score, occupation, cohabitation, marital status, and household income.

Missing answers in leisure time physical activity and occupational physical activity were grouped into a single category and kept in the statistical model (see description of participants with missing information of leisure time physical activity and occupational physical activity in Supplementary material online, *Table S1*).

Furthermore, we performed combined Cox proportional hazards regression analyses on the interplay between leisure time physical activity and occupational physical activity with a common reference (i.e. high leisure time physical activity and low occupational physical activity) on MACE and all-cause mortality with adjustment for age, sex, BMI, smoking, years in school, diabetes, systolic blood pressure, blood pressure medication, dietary preferences, alcohol consumption, COPD by GOLD stage, LDL cholesterol, HDL cholesterol, and triglycerides.

Moreover, we investigated the associations of one level higher leisure time physical activity (or occupational physical activity) with risk of MACE and all-cause mortality, overall and after stratification on several lifestyle, health, living condition and socioeconomic factors in Cox regression models adjusted for age, sex, smoking, BMI, years in school,

Table 1 Baseline characteristics of the 104 046 individuals in the Copenhagen General Population Study free of major adverse cardiovascular events at baseline (784 individuals did not report their physical activity in leisure time)

Characteristic	Physical activity in leisure time				*P*-value
	Low, *N* = 6340	Moderate, *N* = 43 224	High, *N* = 46 681	Very high, *N* = 7017	
Men	2924 (46)	16 689 (39)	21 336 (46)	4667 (67)	<0.0001
Age (years)	56 ± 14	58 ± 13	57 ± 13	54 ± 14	<0.0001
Physical activity at work					<0.0001
Low	2502 (39)	12 404 (29)	14 792 (32)	2596 (37)	
Moderate	1401 (22)	11 418 (26)	10 747 (23)	1346 (19)	
High	839 (13)	6156 (14)	6525 (14)	988 (14)	
Very high	242 (4)	911 (2)	1043 (2)	345 (5)	
Non-responders	1356 (21)	12 335 (29)	13 574 (29)	1742 (25)	
Education					<0.0001
<Middle school	716 (11)	4339 (10)	3695 (8)	502 (7)	
Middle school	2772 (44)	18 293 (42)	16 471 (35)	2320 (33)	
High school	2082 (33)	14 353 (33)	16 667 (36)	2525 (36)	
University	747 (12)	6103 (14)	9740 (21)	1652 (24)	
Years in school	10.4 ± 1.9	10.5 ± 1.9	10.9 ± 1.8	11.0 ± 1.8	<0.0001
Household income					<0.0001
Low	1011 (16)	5814 (14)	4593 (10)	697 (10)	
Moderate	2832 (45)	19 811 (46)	19 265 (42)	2626 (38)	
High	2412 (39)	16 983 (40)	22 354 (48)	3634 (52)	
Longest employment since school					<0.0001
Self-employed	579 (9)	3520 (8)	3966 (9)	817 (12)	
Skilled worker	1177 (19)	8266 (19)	8187 (18)	1301 (19)	
Unskilled worker	816 (13)	3764 (9)	2737 (6)	456 (7)	
Office worker	3406 (54)	25 535 (59)	30 206 (65)	4228 (61)	
Housewife	161 (3)	1352 (3)	886 (2)	79 (1)	
Unemployed or senior citizen	166 (3)	559 (1)	409 (1)	62 (1)	
Cohabitation					<0.0001
Living with spouse/cohabitant	4417 (70)	32 125 (74)	36 221 (78)	5340 (76)	
Living alone	1707 (27)	9928 (23)	9205 (20)	1398 (20)	
Living with others	209 (3)	1128 (3)	1219 (3)	273 (4)	
Marital status					<0.0001
Married/cohabiting	4371 (69)	31 937 (74)	36 009 (77)	5308 (76)	
Unmarried	744 (12)	3227 (7)	3342 (7)	745 (11)	
Separated/divorced	734 (12)	4314 (10)	4331 (9)	655 (9)	
Widow/widower	471 (7)	3681 (9)	2925 (6)	287 (4)	
Smoking					<0.0001
Never smoker	2060 (34)	16 401 (39)	19 573 (44)	3107 (47)	
Former smoker	2116 (35)	16 820 (40)	18 914 (42)	2724 (41)	
Current smoker	1906 (31)	8341 (20)	6249 (14)	785 (12)	
Body mass index (kg/m^2)					<0.0001
<18.5	65 (1)	389 (1)	392 (1)	42 (1)	
18.5–29.9	4223 (67)	34 554 (80)	40 810 (88)	6359 (91)	
≥30	2035 (32)	8212 (19)	5413 (12)	604 (9)	
Adherence to dietary guidelines					<0.0001
Very high	256 (5)	3420 (9)	5140 (12)	681 (10)	
High	544 (10)	6258 (16)	8415 (19)	1229 (19)	
Intermediate	2677 (47)	21 801 (55)	23 813 (55)	3613 (56)	
Low	827 (15)	3573 (9)	2961 (7)	529 (8)	
Very low	1343 (24)	4572 (12)	2834 (7)	440 (7)	

Continued

Table 1 *Continued*

Characteristic	Physical activity in leisure time				*P*-value
	Low, *N* = 6340	Moderate, *N* = 43 224	High, *N* = 46 681	Very high, *N* = 7017	
Alcohol intake (women/men)					<0.0001
Non-drinker	838 (14)	3646 (9)	2830 (6)	521 (8)	
1–14/1–21 drinks/week	3908 (67)	29 891 (73)	34 176 (76)	5141 (76)	
>14/>21 drinks/week	1083 (19)	7506 (18)	8141 (18)	1118 (16)	
Diabetes	399 (6)	1788 (4)	1285 (3)	146 (2)	<0.0001
Systolic blood pressure (mmHg)	139 ± 22	139 ± 21	137 ± 21	135 ± 20	<0.0001
Blood pressure medication	1299 (22)	8335 (21)	6667 (16)	770 (13)	<0.0001
COPD					<0.0001
No COPD	4687 (81)	32 846 (83)	35 482 (85)	5297 (86)	
GOLD stage 1	469 (8)	3502 (9)	4058 (10)	558 (9)	
GOLD stage 2	514 (9)	2600 (7)	1865 (4)	248 (4)	
GOLD stage 3	126 (2)	400 (1)	182 (0)	23 (0)	
GOLD stage 4	23 (0)	58 (0)	21 (0)	2 (0)	
Vital exhaustion score	1.8 ± 1.6	1.2 ± 1.4	0.9 ± 1.2	0.7 ± 1.1	<0.0001
Resting heart rate (bpm)	77 ± 13	74 ± 12	70 ± 12	65 ± 12	<0.0001
HDL cholesterol (mmol/L)	1.45 ± 0.51	1.61 ± 0.52	1.67 ± 0.51	1.63 ± 0.51	<0.0001
LDL cholesterol (mmol/L)	3.30 ± 0.98	3.31 ± 0.96	3.23 ± 0.92	3.13 ± 0.90	<0.0001
Triglycerides (mmol/L)	2.0 ± 1.4	1.7 ± 1.2	1.6 ± 1.0	1.5 ± 1.0	<0.0001

Data are *n* (%) or mean ± SD.
COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

dietary preferences, alcohol, COPD by GOLD stage, systolic blood pressure, blood pressure medication, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, and physical activity at work (or physical activity in leisure time). Test for interactions was conducted by introducing interaction terms in the individual Cox models.

To address the issue of reverse causation, we performed an analysis of the associations between leisure time physical activity and occupational physical activity with MACE and all-cause mortality in models adjusted for age, sex, smoking, BMI, years in school, dietary preferences, alcohol consumption, COPD by GOLD stage, systolic blood pressure, blood pressure medication, diabetes, LDL cholesterol, HDL cholesterol, and triglycerides with start of follow-up 1, 3, and 5 years after baseline.

The assumption of proportionality in the Cox regression models was tested with the Lin *et al.* score process test.[21] Two-sided *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with R, version 3.5.2 (https://cran.r-project.org/).

Results

In the eligible study population, we observed 7913 (7.6%) MACE and 9846 (9.5%) deaths from all causes during the median follow-up period of 10 years (range 0.1–15 years).

Table 1 illustrates lifestyle and other characteristics stratified into low, moderate, high, and very high leisure time physical activity. The level of leisure time physical activity was strongly associated with sex and, to a lesser degree, with age. There was an uneven distribution of occupational physical activity across levels of leisure time physical activity. The prevalence of current smokers, BMI ≥30 kg/m^2, short education, low household income, low adherence to dietary guidelines, COPD GOLD stage 4, and diabetes was highest among the group with low leisure time physical activity. Accordingly, the group with low leisure time physical activity had a higher vital exhaustion score, resting heart rate, LDL cholesterol, and triglycerides compared with the very high leisure time physical activity group.

Table 2 illustrates lifestyle and other characteristics stratified into low, moderate, high, and very high occupational physical activity. The level of occupational physical activity was strongly associated with sex. While more women than men performed moderate and high occupational physical activity, very high occupational physical activity was predominantly performed by men. The age was relatively stable across the groups of occupational physical activity. The very high occupational physical activity group had a higher prevalence of very high leisure time physical activity, current smokers, BMI ≥30 kg/m^2, short education, low adherence to dietary guidelines, and high alcohol consumption per week compared with the low occupational physical activity group.

Figure 1 shows the associations between leisure time physical activity and occupational physical activity with the outcomes MACE and all-cause mortality, respectively. Compared to low leisure time physical activity, multivariable adjusted (for lifestyle, health, living conditions, and socioeconomic factors) hazard ratios for MACE were 0.86 (0.78–0.96) for moderate, 0.77 (0.69–0.86) for high, and 0.85 (0.73–0.98) for very high activity; corresponding values for higher occupational physical activity were 1.04 (0.95–1.14), 1.15 (1.04–1.28), and 1.35 (1.14–1.59), respectively (*Figure 1*, model B). For all-cause

Table 2 Baseline characteristics of the 104 046 individuals in the Copenhagen General Population Study free of major adverse cardiovascular events at baseline (29 481 individuals did not report their physical activity at work, e.g. due to retirement)

Characteristic	Physical activity at work				*P*-value
	Low, *N* = 32 391	Moderate, *N* = 25 032	High, *N* = 14 580	Very high, *N* = 2562	
Men	16 692 (52)	8708 (35)	5599 (38)	2370 (93)	<0.0001
Age (years)	51 ± 10	54 ± 11	51 ± 11	51 ± 11	<0.0001
Physical activity in leisure time					<0.0001
Low	2502 (8)	1401 (6)	839 (6)	242 (9)	
Moderate	12 404 (38)	11 418 (46)	6156 (42)	911 (36)	
High	14 792 (46)	10 747 (43)	6525 (45)	1043 (41)	
Very high	2596 (8)	1346 (5)	988 (7)	345 (13)	
Non-responders	97 (0)	120 (0)	72 (0)	21 (1)	
Education					<0.0001
<Middle school	434 (1)	1140 (5)	956 (7)	353 (14)	
Middle school	7786 (24)	8987 (36)	7195 (49)	1752 (68)	
High school	13 153 (41)	10 834 (43)	5715 (39)	432 (17)	
University	10 947 (34)	4008 (16)	682 (5)	21 (1)	
Years in school	11.6 ± 1.4	11.1 ± 1.7	10.5 ± 1.8	9.5 ± 1.6	<0.0001
Household income					<0.0001
Low	977 (3)	1690 (7)	944 (7)	152 (6)	
Moderate	8529 (27)	9994 (40)	8090 (56)	1599 (63)	
High	22 675 (70)	13 040 (53)	5379 (37)	783 (31)	
Longest employment since school					<0.0001
Self-employed	2601 (8)	2359 (9)	1275 (9)	449 (18)	
Skilled worker	1829 (6)	4467 (18)	5903 (41)	1281 (50)	
Unskilled worker	659 (2)	1431 (6)	2382 (16)	549 (22)	
Office worker	26 773 (83)	15 708 (63)	4624 (32)	254 (10)	
Housewife	122 (0)	743 (3)	223 (2)	2 (0)	
Unemployed or senior citizen	190 (1)	182 (1)	91 (1)	10 (0)	
Cohabitation					<0.0001
Living with spouse/cohabitant	26 380 (82)	19 683 (79)	11 017 (76)	2013 (79)	
Living alone	4989 (15)	4485 (18)	2895 (20)	468 (18)	
Living with others	998 (3)	843 (3)	652 (4)	79 (3)	
Marital status					<0.0001
Married/cohabiting	26 221 (81)	19 573 (78)	10 880 (75)	1963 (77)	
Unmarried	2626 (8)	1890 (8)	1706 (12)	327 (13)	
Separated/divorced	2797 (9)	2435 (10)	1569 (11)	227 (9)	
Widow/widower	696 (2)	1082 (4)	403 (3)	36 (1)	
Smoking					<0.0001
Never smoker	14 561 (47)	10 282 (43)	5336 (38)	776 (31)	
Former smoker	11 931 (39)	9579 (40)	5217 (37)	845 (34)	
Current smoker	4196 (14)	4146 (17)	3460 (25)	848 (34)	
Body mass index (kg/m^2)					<0.0001
<18.5	236 (1)	250 (1)	125 (1)	9 (0)	
18.5–29.9	27 760 (86)	21 124 (85)	12 022 (83)	1924 (75)	
≥30	4343 (13)	3609 (14)	2408 (17)	626 (24)	
Adherence to dietary guidelines					<0.0001
Very high	2899 (9)	2618 (11)	1184 (9)	40 (2)	
High	5470 (18)	4309 (19)	1988 (15)	179 (8)	
Intermediate	17 618 (58)	12 658 (55)	7095 (53)	1090 (48)	
Low	2466 (8)	1778 (8)	1394 (11)	385 (17)	
Very low	2072 (7)	1737 (8)	1613 (12)	565 (25)	

Continued

Table 2 *Continued*

Characteristic	Physical activity at work				*P*-value
	Low, *N* = 32 391	Moderate, *N* = 25 032	High, *N* = 14 580	Very high, *N* = 2562	
Alcohol intake (women/men)					<0.0001
Non-drinker	1869 (6)	1886 (8)	1560 (11)	203 (8)	
1–14/1–21 drinks/week	24 598 (78)	18 081 (75)	10 074 (74)	1651 (67)	
>14/>21 drinks/week	4871 (16)	4017 (17)	2025 (15)	609 (25)	
Diabetes	650 (2)	663 (3)	336 (2)	80 (3)	<0.0001
Systolic blood pressure (mmHg)	133 ± 19	135 ± 20	134 ± 20	139 ± 19	<0.0001
Blood pressure medication	3181 (11)	3288 (14)	1436 (11)	283 (12)	<0.0001
COPD					<0.0001
No COPD	25 929 (90)	19 720 (87)	11 711 (88)	2076 (87)	
GOLD stage 1	1874 (6)	1756 (8)	962 (7)	169 (7)	
GOLD stage 2	936 (3)	956 (4)	609 (5)	129 (5)	
GOLD stage 3	79 (0)	108 (0)	58 (0)	14 (1)	
GOLD stage 4	18 (0)	12 (0)	5 (0)	1 (0)	
Vital exhaustion score	1.1 ± 1.3	1.1 ± 1.3	1.2 ± 1.3	1.2 ± 1.3	<0.0001
Resting heart rate (bpm)	69 ± 12	72 ± 12	73 ± 12	73 ± 12	<0.0001
HDL cholesterol (mmol/L)	1.56 ± 0.49	1.65 ± 0.51	1.60 ± 0.50	1.43 ± 0.46	<0.0001
LDL cholesterol (mmol/L)	3.24 ± 0.92	3.28 ± 0.94	3.23 ± 0.93	3.34 ± 0.94	<0.0001
Triglycerides (mmol/L)	1.6 ± 1.1	1.6 ± 1.1	1.6 ± 1.1	2.0 ± 1.8	<0.0001

Data are *n* (%) or mean ± SD.
COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

mortality, corresponding hazard ratios for higher leisure time physical activity were 0.74 (0.68–0.81), 0.59 (0.54–0.64), and 0.60 (0.52–0.69), and for higher occupational physical activity 1.06 (0.96–1.16), 1.13 (1.01–1.27), and 1.27 (1.05–1.54), respectively. The sensitivity analyses with adjustments for a range of additional potential confounders (*Figure 1*, model C) found similar associations for both leisure time and occupational physical activity with risk of MACE and all-cause mortality.

Figure 2 illustrates the interplay between four leisure time physical activity categories and four occupational physical activity categories in the multivariable model with adjustment for lifestyle, health, living conditions, and socioeconomic factors with the common reference category (i.e. high leisure time physical activity and low occupational physical activity) with the lowest risks of MACE and all-cause mortality. There was no evidence of interaction between leisure time and occupational physical activity on risk of MACE ($P = 0.40$) or all-cause mortality ($P = 0.31$), implying that risk of both endpoints increased with higher occupational physical activity and with lower leisure time physical activity, independent of the level of each other. Accordingly, we found a general tendency of a higher risk for both outcomes with higher levels of occupational physical activity across the levels of leisure time physical activity. For the low and moderate levels of occupational physical activity, higher levels of leisure time physical activity were clearly associated with lower risk for both outcomes. For the high and very high levels of occupational physical activity, less clear associations for both outcomes with higher levels of leisure time physical activity were seen. However, the statistical power in these groups was modest due to relatively low number of individuals and events.

Figures 3 and 4 show multivariable adjusted hazard ratios per one level higher leisure time or occupational physical activity on risk of MACE and all-cause mortality, overall and after stratification into 20 lifestyle, health, living condition, and socioeconomic factors. Consistent reduced and increased hazard ratios for higher levels of leisure time and occupational physical activity, respectively, were observed in strata of all covariates; there was no convincing evidence of interaction between leisure time or occupational physical activity and the 20 lifestyle, health, living condition, and socioeconomic factors on risk of MACE or all-cause mortality, which implies that the overall findings did not differ in the different strata (*Figures 3 and 4*; $*P > 0.05$ after correction for 4 × 20 multiple comparison according to the Bonferroni method; required $P < 0.05/40$ or $P < 0.001$).

Figure 5 shows the associations between leisure time physical activity and occupational physical activity with the outcomes MACE and all-cause mortality, respectively, adjusted for age, sex, smoking, BMI, years in school, dietary preferences, alcohol consumption, COPD by GOLD stage, systolic blood pressure, blood pressure medication, diabetes, LDL cholesterol, HDL cholesterol, and triglycerides in models with the start of follow-up 1, 3, and 5 years after baseline. The results are in line with estimates reported in the main statistical model presented in *Figure 1*.

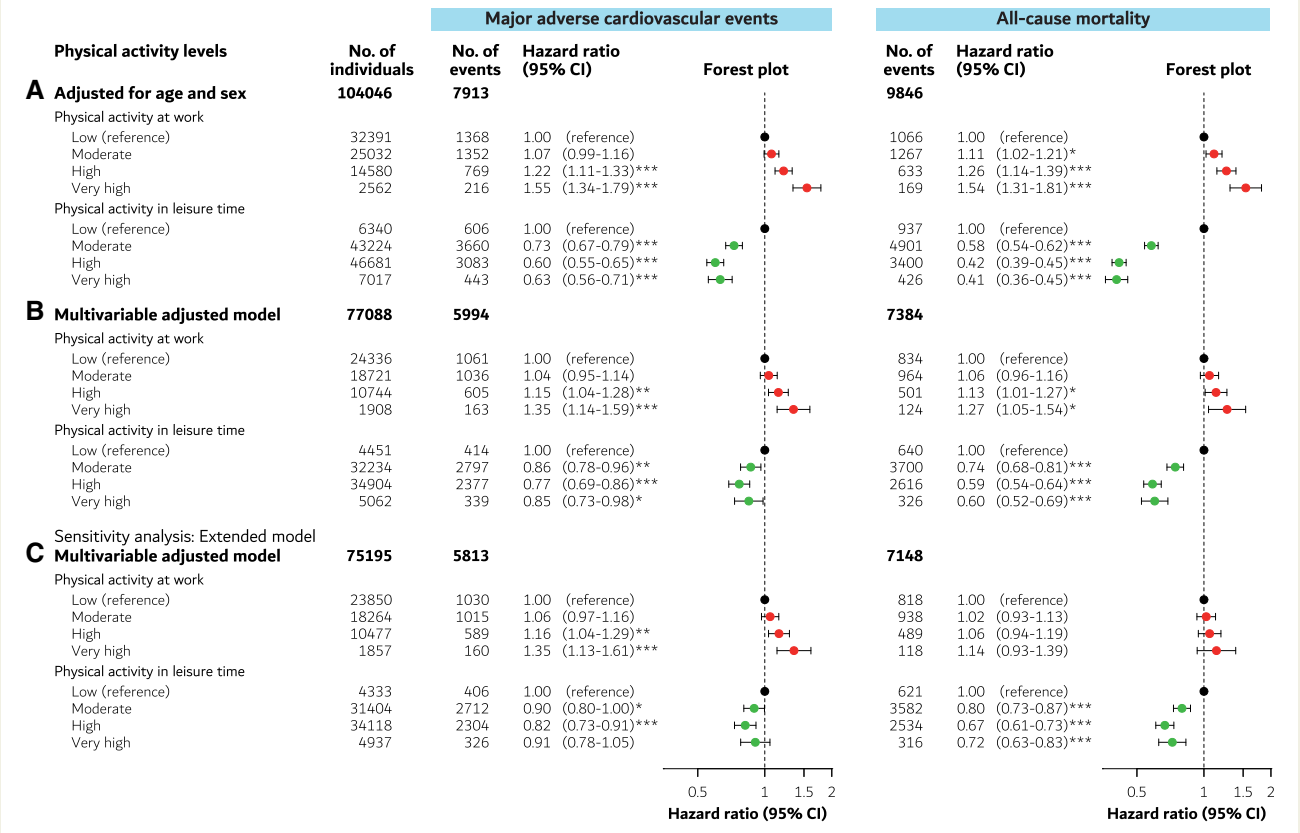


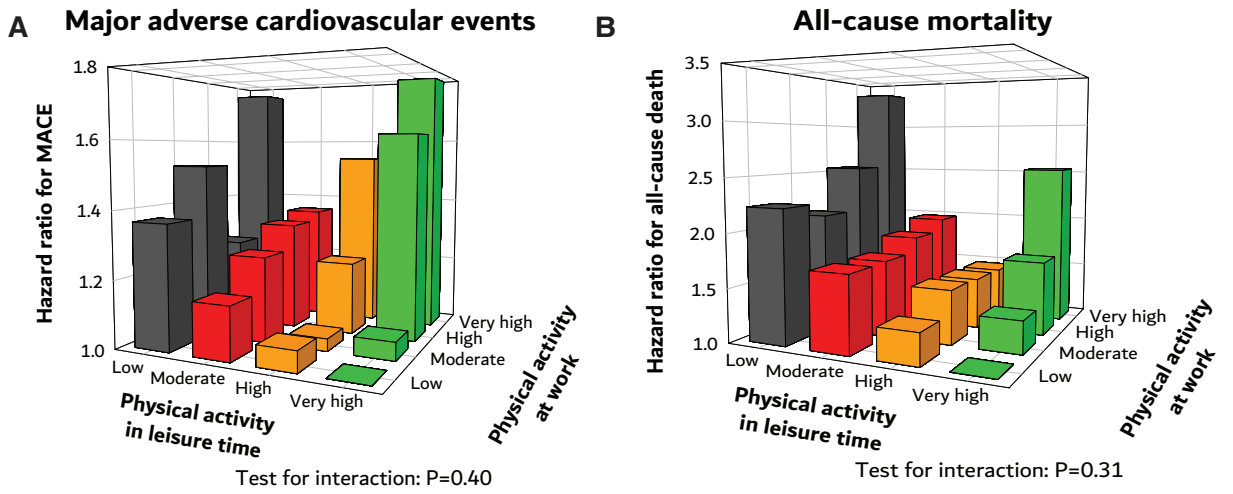
Figure 1 Associations of leisure time physical activity and occupational physical activity with risk of major adverse cardiovascular events and all-cause mortality. Cox regression models were adjusted for: model A, age and sex; model B, model A + body mass index, smoking, years in school, diabetes, systolic blood pressure, blood pressure medication, dietary preferences, alcohol consumption, chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease stage, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; and an extended multivariable sensitivity model C, model B + resting heart rate, vital exhaustion score, occupation, cohabitation, marital status, and household income. The analyses were based on individuals from the Copenhagen General Population Study with a median follow-up of 10 years. CI, confidence interval. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Discussion

In 104 046 individuals from the Copenhagen General Population Study with 7913 MACE and 9846 deaths during 10 years of follow-up, we observed that higher leisure time physical activity was associated with reduced risk of MACE and all-cause mortality while higher occupational physical activity was associated with increased risks, independent of each other. The novel demonstration of the independent association of the two domains of physical activity with risk of MACE and all-cause mortality supports the physical activity paradox.

Mechanistically, leisure time physical activity is generally shown to cause improved cardiorespiratory and metabolic fitness and health, while the characteristics of occupational physical activity are predominantly associated with fatigue, insufficient recovery, elevated 24-h blood pressure, and heart rate without improvements in cardiorespiratory fitness and health.[14] For example, a recent study found leisure time physical activity to be beneficially associated with the systemic inflammation marker high-sensitivity C-reactive protein, but occupational physical activity to be associated with detrimental levels.[22] The physical activity paradox is suggested to be explained by the different characteristics of physical activity during work and leisure time, where leisure time physical activity primarily comprises dynamic activities of higher intensity and shorter durations, while occupational physical activity is composed of more static and constrained activities of lower intensity and long durations.[14] Further investigation of the association between occupational physical activity and health was recently encouraged by the World Health Organization (WHO) guidelines on physical activity and sedentary behaviour to improve our understanding and evidence based on the potential domain-specific effects of physical activity on health.[2,23]

We found beneficial dose–response associations for MACE and all-cause mortality with higher levels of leisure time physical activity in the fully adjusted models. This finding of a strong beneficial association of MACE and all-cause mortality with high leisure time physical activity is in accordance with many previous studies[1,2] and supports the importance of high leisure time physical activity for preventing MACE and premature mortality. In contrast, we observed a harmful association for MACE and all-cause mortality with higher levels of occupational physical activity in the model adjusted for lifestyle, health, living conditions, and socioeconomic factors (*Figure 1*, model B). This finding remained in the model with adjustments for additional potential lifestyle, health, living condition, and socioeconomic confounders



Hazard ratio (95% confidence interval) for major adverse cardiovascular events

Physical activity at work	Physical activity in leisure time			
	Low	Moderate	High	Very high
Very high	1.76 (1.01-3.07)	1.35 (0.94-1.96)	1.54 (1.08-2.19)	1.80 (1.11-2.92)
High	1.26 (0.83-1.92)	1.33 (1.00-1.77)	1.22 (0.91-1.62)	1.62 (1.09-2.40)
Moderate	1.52 (1.07-2.15)	1.25 (0.95-1.65)	1.04 (0.78-1.37)	1.05 (0.69-1.60)
Low	1.37 (0.99-1.87)	1.16 (0.88-1.52)	1.06 (0.81-1.40)	1.00 (reference)

Number of individuals/major adverse cardiovascular events

Physical activity at work	Physical activity in leisure time			
	Low	Moderate	High	Very high
Very high	171/16	687/56	785/67	254/23
High	578/36	4528/269	4884/252	704/44
Moderate	998/74	8619/571	8082/351	958/35
Low	1830/117	9422/468	11113/410	1905/58

Hazard ratio (95% confidence interval) for all-cause mortality

Physical activity at work	Physical activity in leisure time			
	Low	Moderate	High	Very high
Very high	3.34 (1.81-6.17)	1.97 (1.22-3.18)	1.46 (0.89-2.40)	2.53 (1.42-4.51)
High	2.54 (1.56-4.13)	1.85 (1.23-2.78)	1.47 (0.98-2.23)	1.69 (0.99-2.87)
Moderate	2.11 (1.34-3.32)	1.71 (1.15-2.54)	1.50 (1.00-2.24)	1.30 (0.74-2.26)
Low	2.23 (1.46-3.41)	1.71 (1.15-2.54)	1.29 (0.86-1.93)	1.00 (reference)

Number of individuals/all-cause deaths

Physical activity at work	Physical activity in leisure time			
	Low	Moderate	High	Very high
Very high	171/17	687/47	785/39	254/21
High	578/45	4528/231	4884/190	704/29
Moderate	998/67	8619/544	8082/318	958/24
Low	1830/127	9422/418	11113/257	1905/26

Figure 2 Interplay between four leisure time physical activity categories and four occupational physical activity categories on risk of (*A*) major adverse cardiovascular events and (*B*) all-cause mortality. Cox regression models were adjusted for age, sex, body mass index, smoking, years in school, diabetes, systolic blood pressure, blood pressure medication, dietary preferences, alcohol consumption, chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease stage, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. The common reference category (i.e. high leisure time physical activity and low occupational physical activity) had the lowest risk of major adverse cardiovascular events and all-cause mortality. The analyses were based on individuals from the Copenhagen General Population Study with a median follow-up of 10 years.

(*Figure 1*, model C), and across groups of individuals with different lifestyle, health, living condition, and socioeconomic factors (*Figures 3 and 4*), as well as when excluding individuals dying within the first 5 years of follow-up (*Figure 5*). Our finding of harmful associations of higher levels of occupational physical activity with increased risk of MACE and all-cause mortality is in line with recent prospective studies.[3–5] A recent systematic review found that men, but not women, with high occupational physical activity had 18% increased risk of all-cause mortality.[11] However, as shown by a recent umbrella review, no consistent association between occupational physical activity and various health outcomes was found.[12] Thus, there is a need for better quality evidence to provide a unequivocal statement on the health effects of occupational physical activity.[12] Our study meets this need.

The main criticism to previous studies finding an increased risk for cardiovascular morbidity and all-cause mortality associated with high occupational physical activity has been the potential risk for insufficient adjustment for confounding factors, such as socioeconomic class.[24] To meet these limitations, we did a sensitivity analyses with adjustments for a long list of potential confounding factors in the association between physical activity and health, such as age, sex, BMI, smoking, years in school, diabetes, systolic blood pressure, blood pressure medicine, dietary preferences, alcohol intake, LDL cholesterol, HDL cholesterol, triglycerides, resting heart rate, vital exhaustion score, COPD by GOLD stage, occupation, cohabitation, marital status, and household income. This did not change the main finding. Moreover, we found consistent decreased risk associated with higher levels of leisure time physical activity and increased risk associated with higher levels of occupational physical activity across strata of 20 potential lifestyle, health, living condition, and socioeconomic confounders. For both leisure time physical activity and occupational physical activity, we found no convincing evidence of interaction with the 20 lifestyle, health, living conditions, and socioeconomic factors and the health outcomes on risk of MACE and all-cause mortality, indicating that the overall findings did not differ across subgroups. Furthermore, the risk estimates remained similar when excluding participants dying within 1, 3, and 5 years of follow-up, suggesting no

Figure 3 Association of one level higher leisure time physical activity (*A*) or occupational physical activity (*B*) with risk of major adverse cardiovascular events overall and after stratification on 20 lifestyle, health, living condition, and socioeconomic factors. Cox regression models adjusted for age, sex, smoking, body mass index, years in school, dietary preferences, alcohol, chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease stage, systolic blood pressure, blood pressure medication, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and physical activity at work or physical activity in leisure time. *$P > 0.05$ after correction for 2×40 (*Figure 4*) multiple comparison according to the Bonferroni method (required $P < 0.05/40$ or $P < 0.001$). The analyses were based on individuals from the Copenhagen General Population Study with a median follow-up of 10 years. CI, confidence interval.

major influence of reverse causation on our results (*Figure 5*). However, we acknowledge that reverse causation can always be an issue in observational studies. These findings support that the physical activity paradox is not just a matter of insufficient adjustments for confounding factors or reverse causation.

Moreover, the analyses of the interplay between four leisure time physical activity categories and four occupational physical activity categories (*Figure 2*) showed that the group with the combination of high leisure time physical activity and low occupational physical activity had the lowest risk of MACE and all-cause mortality. Importantly, we found no evidence of interaction between leisure time and occupational physical activity on risk of MACE ($P = 0.40$) or all-cause mortality ($P = 0.31$). This result implies that the risk of both endpoints increased with higher occupational physical activity and with lower leisure time physical activity, independent of the level of each other. The previous studies investigating the interplay between occupational

Figure 4 Association of one level higher leisure time physical activity (*A*) or occupational physical activity (*B*) with risk of all-cause mortality, overall and after stratification on 20 lifestyle, health, living condition, and socioeconomic factors. Cox regression models adjusted for age, sex, smoking, body mass index, years in school, dietary preferences, alcohol, chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease stage, systolic blood pressure, blood pressure medication, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and physical activity at work. *$P > 0.05$ after correction for 2×40 (*Figure 3*) multiple comparison according to the Bonferroni method (required $P < 0.05/40$ or $P < 0.001$). The analyses were based on individuals from the Copenhagen General Population Study with a median follow-up of 10 years. CI, confidence interval.

and leisure time physical activity on cardiovascular disease and mortality are relatively few, had lower statistical power than the present study and reported varying findings.[8,25,26] Thus, to help establish recommendations on leisure time physical activity particularly among adults with high levels of occupational physical activity, we need further research on the potential independent association of leisure time and occupational physical activity with risk of cardiovascular disease and all-cause mortality.

Work constitutes the main domain for physical activity for a large fraction of the adult population worldwide.[15,16] We are not aware of

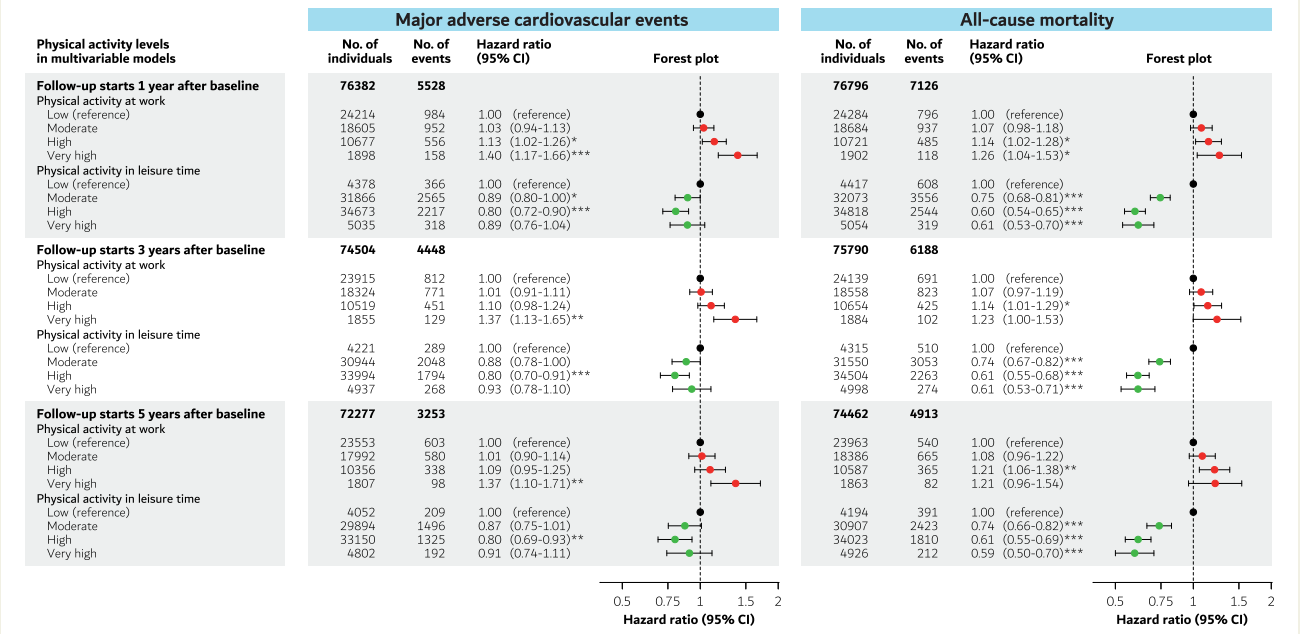


Figure 5 Associations of leisure time physical activity and occupational physical activity with risk of major adverse cardiovascular events and all-cause mortality with start of follow-up 1, 3, and 5 years after baseline, respectively. Cox regression models were adjusted for age, sex, body mass index, smoking, years in school, diabetes, systolic blood pressure, blood pressure medication, dietary preferences, alcohol consumption, chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease stage, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. The analyses were based on individuals from the Copenhagen General Population Study with a median follow-up of 10 years. CI, confidence interval. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

any international or national physical activity guidelines differentiating on occupational physical activity and leisure time physical activity.[1,2] If the physical activity paradox holds true, this can contribute to the understanding and interventions on the generally poor health of individuals with high occupational physical activity. Thus, we applaud the recent WHO guidelines for physical activity and sedentary behaviour to take the physical activity paradox into consideration and request further research on the domain of physical activity on health.[2]

Strengths and limitations

A methodological strength of this study is the large general population study permitting sufficient statistical power to investigate associations of both occupational physical activity and leisure time physical activity with MACE and all-cause mortality using multivariable adjusted models. Moreover, the possibility to perform subgroup analyses is a methodological strength for further investigation of potential confounding. A methodological limitation of this study is that information of both leisure time physical activity and occupational physical activity is based on self-assessment, which may entail some degree of misclassification. The questions used for measuring both leisure time physical activity and occupational physical activity have been used for decades in several cohorts, and because they are very similar in content and wording, the questions cannot explain the different characteristics of physical activity at work and leisure time being the potential underlying reason to the contrasting associations of leisure time physical activity and occupational physical activity with risk of MACE and all-cause mortality in the present study. It is also a limitation that the participation rate in our study was 43%, which is lower than in many cohorts examined 30–40 years ago; however, this is a general tendency in contemporary cohort studies globally, likely due to the higher number of requests to participate in surveys and other studies today compared to 30–40 years ago.

The group with sedentary work could theoretically be expected to have an increased risk for cardiovascular disease and all-cause mortality. However, we found this group to have the lowest risk. Our observation is in line with previous studies showing that it is particularly sitting during leisure time (particularly TV viewing) that is associated with increased cardiovascular disease and all-cause mortality risk, and that occupational sitting is not associated with a similar increased risk.[27,28] This can likely be explained by a different time-pattern and behaviour of sitting during work and leisure,[29] where for example abruption during sitting is more likely to occur at work (e.g. regular breaks, walk to meeting/printer) than during leisure time. As our findings represent observational associations, it is not possible to infer causality from our data. The study sample was from the general population of Whites of Danish descent from the greater Copenhagen area in Denmark including both high- and low-income areas and might thus not be generalizable to all other countries in Europe and elsewhere. Because the working conditions (i.e. the prevalence of high occupational physical activity such as heavy lifting at work), living environment, and lifestyle in Denmark are generally more advanced than in some Southern and Eastern European

countries,[30] the observed harmful health associations from occupational physical activity can potentially be even stronger in these countries than observed in the present study. The results might therefore not be directly generalizable to all other countries, and we recommend researchers to perform studies on the physical activity paradox in particularly low-income and less-privileged populations.

Conclusion

Higher leisure time physical activity is associated with reduced risk of MACE and all-cause mortality while higher occupational physical activity is associated with increased risks, independent of each other. The novel demonstration of the independent association of the two types of physical activity on risk of MACE and all-cause mortality supports the physical activity paradox. These findings may be considered by those writing guidelines on cardiovascular disease prevention in relation to physical activity.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The Danish Data protection Agency does not allow open access to our data; however, upon reasonable request the steering committee of the Copenhagen General Population Study may allow further follow-up analyses.

Conflict of interest: The authors declare to have no conflict of interest.

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