Original research

Leisure-time and occupational physical activity and health outcomes in cardiovascular disease

Nadia E Bonekamp,[1] Frank L J Visseren ,[1] Ynte Ruigrok,[2] Maarten J M Cramer,[3] Gert Jan de Borst,[4] Anne M May,[5] Charlotte Koopal,[1] on behalf of the UCC-SMART Study group

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For numbered affiliations see end of article.

Correspondence to
Dr Frank L J Visseren, Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, PO Box 85500, 3508 GA, The Netherlands;
F.L.J.Visseren@umcutrecht.nl

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ABSTRACT

Objective In healthy populations, leisure-time physical activity (LTPA) improves health outcomes, while, paradoxically, occupational physical activity (OPA) is associated with detrimental health effects. This study aimed to investigate the associations of LTPA and OPA with mortality, cardiovascular events and type 2 diabetes (T2D) in patients with cardiovascular disease (CVD).

Methods In 7058 outpatients with CVD (age 61±10 years, 75% male) from the prospective Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease cohort, Cox models were used to quantify the associations between self-reported LTPA and OPA and all-cause mortality, cardiovascular events and T2D.

Results Over 8.6 years (IQR: 4.6–12.5) of follow-up, 1088 vascular events, 1254 deaths and 447 incident T2D cases occurred. The top LTPA quarter had a lower risk of all-cause mortality (HR 0.63, 95% CI 0.54 to 0.74), recurrent cardiovascular events (HR 0.72, 95% CI 0.60 to 0.84) and incident T2D (HR 0.71, 95% CI 0.55 to 0.93), compared with the lowest quarter. The continuous LTPA associations were reverse J-shaped for all-cause mortality and vascular events and linear for T2D. OPA (heavy manual vs sedentary) showed a trend towards an increased risk of all-cause mortality (HR 1.08, 95% CI 0.86 to 1.35), cardiovascular events (HR 1.15, 95% CI 0.91 to 1.45) and T2D (HR 1.04, 95% CI 0.72 to 1.50). The detrimental effects of higher OPA were more pronounced in men, never-smokers, people with higher education and active employment.

Conclusions In patients with CVD, LTPA was associated with lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D. In contrast, OPA seemed to increase the risk of these outcomes. These findings support the existence of a physical activity paradox in patients with CVD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In apparently healthy populations, leisure-time physical activity and occupational physical activity have opposite health effects: while leisure-time physical activity is associated with reduced risk of all-cause mortality and cardiovascular events, occupational physical activity increases these risks. This physical activity paradox may be more pronounced in patients with cardiovascular disease, due to pathophysiological changes after cardiovascular events.

WHAT THIS STUDY ADDS

⇒ This study shows that leisure-time physical activity has a strong protective association with all-cause mortality (HR 0.63, 95% CI 0.54 to 0.74), cardiovascular events (HR 0.72, 95% CI 0.60 to 0.84) and type 2 diabetes risk (HR 0.71, 95% CI 0.55 to 0.93) in patients with cardiovascular disease, while physical activity at work might be associated with unfavourable health effects in this population (HRs around 1.10 with 95% CI including 1.00, for the three outcomes).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that physical activity at work does not provide similar health benefits as leisure-time physical activity and may even have harmful effects for patients with cardiovascular disease. For clinical practice, our results indicate that physical activity at work should not be regarded as a substitute for physical activity in leisure time.

Linked

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INTRODUCTION

Physical activity has extensively been shown to reduce the risk of cardiovascular disease (CVD) in apparently healthy individuals[1] and is a key recommendation in guidelines for CVD prevention and treatment.[2 3] Physical activity's benefits result from reducing inflammation and improving cardiorespiratory fitness[4 5] as well as attenuation of traditional cardiovascular risk factors such as systolic blood pressure and lipid profile.[6 7]

Physical activity can be categorised into occupational physical activity (OPA), comprising all work-related activities, and leisure-time physical activity (LTPA), comprising all activities outside the workspace, such as sport and transport-related activities like walking. In apparently healthy populations, higher LTPA confers relative risk reductions for all-cause mortality (up to 35%),[8] CVD (up to 55%)[9] and type 2 diabetes (T2D) (up to 30%).[9 10] In contrast, increased OPA does not unequivocally show such benefits, with some studies even indicating that more physically demanding OPA increases CVD risk, especially in

men.[11–14] This contradiction in the effects of LTPA and OPA has been called the physical activity paradox.[12]

LTPA and OPA may affect patients with CVD differently than patients from the general population. LTPA is commonly regarded as beneficial for atherosclerotic plaque stability, but OPA has been associated with an increased rate of plaque progression.[15 16] Evidence from subgroup analyses of observational studies indicates that LTPA reduces CVD and all-cause mortality risk in patients with a history of CVD.[17 18] On the other hand, CVD subgroups in observational studies on OPA show that physically demanding OPA might be associated with an increased risk of cardiovascular events and mortality and even show that higher LTPA could have a detrimental effect in patients with CVD with physically demanding OPA.[16]

In this study, we investigated the associations between LTPA and OPA and risk of all-cause mortality, recurrent cardiovascular events and incident T2D in patients with a history of CVD.

METHODS

Study population

Data were used from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial Disease (UCC-SMART) Study, an ongoing single-centre prospective cohort comprising patients aged 18–79 years with cardiovascular risk factors or established CVD.[19] For the current study, data were used from 7058 patients, included in the cohort between January 2002 and December 2019 with established coronary artery disease, peripheral artery disease (PAD) or cerebrovascular disease (CeVD) at inclusion in the cohort. Analyses on T2D incidence were limited to participants without T2D at baseline (N=5765, online supplemental figure 1).

Baseline measurements

Upon inclusion in the UCC-SMART cohort, participants completed a standardised questionnaire on medical history, cardiovascular risk factors and medication use. Patients underwent physical examination, and laboratory measurements were performed.

LTPA and OPA were self-reported in the baseline questionnaire. LTPA was defined as activity from sports, walking, cycling and gardening and was assessed using validated ranking physical activity questionnaire[20] with an additional question on sport activity. LTPA was expressed as metabolic equivalent of task hours per week (METh/wk). METh/wk combines intensity and duration of the activity by multiplying the reported weekly hours of physical activity with activity-specific MET intensity obtained from the Compendium of Physical Activity.[21] To exemplify: a participant who walks (estimated at 3.5 MET) 2 hours per week would perform (2×3.5)=7.0 METh/wk. OPA was quantified using a question with four intensity levels that assessed the physical activity intensity during participants' last active employment. These four levels were: predominantly sedentary work, standing work, manual work and heavy manual work.

Clinical outcomes

Participants were sent biannual follow-up questionnaires on vital status and the occurrence of cardiovascular events. When participants reported an event, additional information was obtained from the treating physician or hospital. The endpoint classification was made independently by three physicians in accordance with previously published definitions.[19]

The primary outcomes were all-cause mortality, recurrent cardiovascular events and incident T2D. Recurrent cardiovascular events were a composite of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular mortality. The individual components of the vascular composite endpoint were assessed as secondary endpoints.

Data analyses

Baseline characteristics were reported stratified for quarters of the LTPA distribution and OPA categories. Categorical variables were presented as frequencies with percentages and continuous variables as means with SD or medians with IQR. Multivariable-adjusted Cox models with time-on-study as time scale were used to estimate the associations for LTPA and OPA. Patients who were lost to follow-up (N=446, 6%) were censored on the last

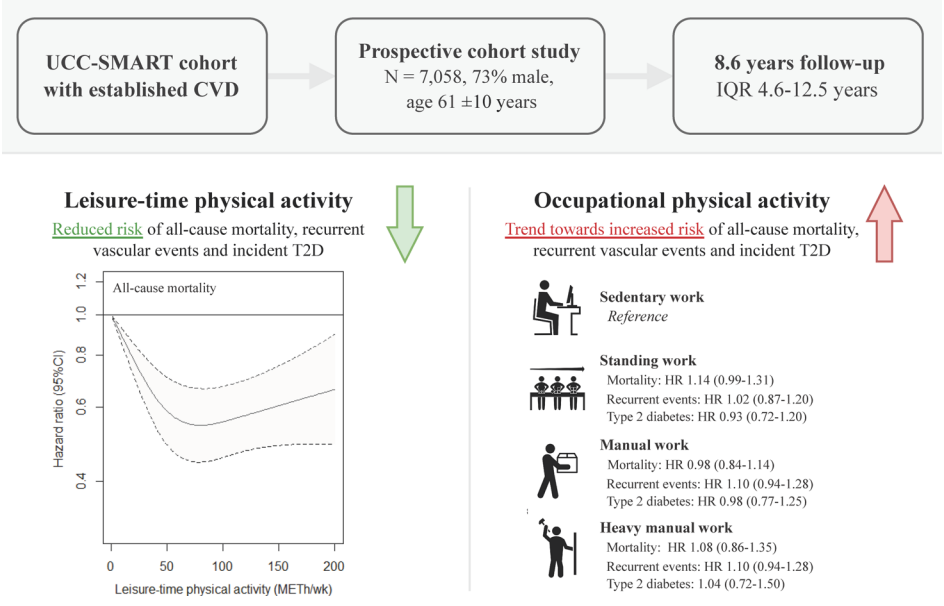

Figure 1 Central figure of study design and key findings. CVD, cardiovascular disease; METh/wk, metabolic equivalent of task hours per week; T2D, type 2 diabetes; UCC-SMART, Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease.

day their status was known. The proportional hazard assumption was checked by visual inspection of Schoenfeld residuals. Model 1 adjusted for age and sex. Model 2 adjusted for model 1, smoking status, number of pack years and alcohol use. Model 3, the main model, additionally adjusted for education level and employment status. In model 4, further adjustments were made for variables that could be either confounders or intermediates: T2D, body mass index (BMI), systolic blood pressure and low-density lipoprotein cholesterol (LDL-C). The models for LTPA and OPA were not mutually adjusted for each other. The associations of LTPA as a continuous variable were assessed using restricted cubic splines with three knots in Cox models adjusted for the covariates in model 3.

Interplay between LTPA and OPA was assessed by comparing the effect of different combinations of LTPA and OPA against a common reference (ie, LTPA quarter 1 and sedentary OPA). Sex, age, education, employment status, type of pre-existing CVD, presence of metabolic syndrome, BMI, systolic blood pressure and LDL-C levels were assessed as potential effect modifiers. Effect modification was tested by introducing multiplicative interaction terms into the Cox models. Bonferroni correction was used to account for multiple testing. Subgroup analyses based on strata of sex, smoking status and employment status were run. To assess the impact of reverse causation, the primary analyses were repeated with removal of the first 1, 3 and 5 years of follow-up.

Missing data on LTPA (1%), OPA (7%), education (33%), metabolic syndrome (1%), smoking status (1%), alcohol consumption (1%) and LDL-C levels (7%) were imputed with single imputation using predictive mean matching. A complete case analysis was run to assess the robustness of the imputation. All statistical analyses were performed using R statistical software, V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Figure 1 summarises the study design and key findings.

Baseline characteristics

Patients with higher levels of LTPA were more frequently men (top vs lowest LTPA quarter, 77% vs 69%), more often had a history of coronary artery disease (68% vs 60%), were less likely to smoke (24% vs 35%) and reported more physically demanding OPA (35% (heavy) manual OPA vs 28%, table 1). Patients with more physically demanding OPA had lower education levels, were more frequently smokers and had a higher BMI (online supplemental table 1). Participants with active employment were younger than those who were not actively employed, but otherwise had similar distributions of baseline characteristics.

Association between LTPA and risk of all-cause mortality, recurrent cardiovascular events and incident T2D

Over a follow-up of 8.6 years (IQR: 4.6–12.5 years), 1254 patients (18%) died and 1088 patients (15%) experienced a recurrent cardiovascular event. Incident T2D was diagnosed in 447 participants (8%). For all-cause mortality and recurrent cardiovascular events, LTPA showed a reverse J-shaped association and the association with incident T2D risk was approximately linear (figure 2). Compared with the lowest LTPA quarter, participants in the highest quarter had a lower risk of all-cause mortality (HR 0.63, 95% CI 0.54 to 0.74), recurrent cardiovascular events (HR 0.72, 95% CI 0.60 to 0.84) and incident T2D (HR 0.72, 95% CI 0.55 to 0.93, table 2). The decreased risk of recurrent cardiovascular events was driven by cardiovascular mortality (HR 0.54, 95% CI 0.42 to 0.69, LTPA Q4 vs Q1) and non-fatal stroke (HR 0.87, 95% CI 0.64 to 1.17, online supplemental figure 2/online supplemental table 2). LTPA was associated with a slightly increased risk of non-fatal MI (HR 1.06 95% CI 0.91 to 1.24, online supplemental figure 2/online supplemental table 2).

Association between OPA and risk of all-cause mortality, recurrent cardiovascular events and incident T2D

For all-cause mortality and recurrent cardiovascular events, there was an increased risk in the groups with higher OPA (HR 1.08, 95% CI 0.86 to 1.35 and HR 1.15, 95% CI 0.91 to 1.45, respectively, heavy manual vs sedentary, table 3). Standing work conferred an increased risk of all-cause mortality (HR 1.14, 95% CI 0.99 to 1.31 vs sedentary) and manual work conferred an increased risk of recurrent cardiovascular events (HR 1.10, 95% CI 0.94 to 1.28 vs sedentary). Heavy manual work was associated with a higher non-fatal stroke risk (HR 1.66, 95% CI 1.10 to 2.50 vs sedentary, online supplemental table 2). OPA was not associated with incident T2D (table 3).

Effect modification

Figure 3 shows the interaction between LTPA and OPA. For all-cause mortality and T2D, higher levels of LTPA were associated with a lower risk regardless of OPA level. For recurrent cardiovascular events, the protective association of LTPA was not present in participants with (heavy) manual work. When looking at the different components of recurrent vascular events, this effect modification of (heavy) manual OPA on LTPA was most pronounced in the associations with non-fatal MI and stroke (online supplemental figure 3).

Figure 4 shows the associations between LTPA and OPA across strata of potential effect modifiers. LTPA was strongly associated with risk reductions in patients with multiple CVD types and PAD, but had smaller effects in patients with a history of coronary disease, CeVD or abdominal aortic aneurysm. Across age strata, the association between LTPA and recurrent vascular events was stronger for patients aged 60 years or older.

The associations of OPA with all-cause mortality and recurrent events differed across sex strata, with a protective association of heavy manual OPA in women and a detrimental effect in men (figure 4A,B). Similarly, the associations differed across strata of pre-existing CVD type: protective associations were found for people with PAD and harmful associations were found for people with CeVD. For patients with multiple CVD manifestations, higher OPA was associated with reduced risk of recurrent cardiovascular events (HR 0.58, 95% CI 0.33 to 1.00), while there was no association for patients with a single CVD type. The associations for OPA were stronger for people with a higher education level, with a recurrent events HR of 1.48 (95% CI 0.52 to 4.23) for heavy manual work in highly educated participants compared with an HR of 1.10 (95% CI 0.88 to 1.88) in participants with lower education.

Subgroup and sensitivity analyses

In never-smokers, higher LTPA was associated with a lower risk of all-cause mortality and recurrent cardiovascular events compared with the full population, with HR 0.56 (95% CI 0.38 to 0.83) for all-cause mortality and HR 0.45 (95% CI 0.29 to 0.71) for recurrent vascular events (online supplemental table 4). Conversely, OPA seemed to be associated with increased risk of

Table 1 Baseline characteristics stratified for LTPA

Characteristic	Overall N=7058	LTPA level			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
		0–24 METh/wk	24–43 METh/wk	43–71 METh/wk	71–356 METh/wk
		N=1765	N=1767	N=1763	N=1763
Male sex	5144 (73)	1214 (69)	1268 (72)	1299 (74)	1363 (77)
Age (years)	61±10	60±11	60±10	60±10	61±10
Occupational physical activity					
Sedentary	3558 (50)	914 (52)	979 (55)	940 (53)	725 (41)
Standing	1449 (21)	345 (20)	346 (20)	356 (20)	402 (23)
Manual work	1605 (23)	394 (22)	364 (21)	377 (21)	470 (27)
Heavy manual work	446 (6)	112 (6)	78 (4)	90 (5)	166 (9)
Education					
Low	1927 (27)	551 (31)	450 (26)	445 (25)	481 (27)
Middle	3008 (43)	761 (43)	726 (41)	730 (41)	791 (45)
High	2123 (30)	453 (26)	591 (33)	588 (33)	491 (28)
History of CAD	4551 (65)	1062 (60)	1124 (64)	1167 (66)	1198 (68)
History of CeVD	2053 (29)	544 (31)	552 (31)	477 (27)	480 (27)
History of PAD	1003 (14)	342 (19)	251 (14)	214 (12)	196 (11)
History of AAA	481 (7)	154 (9)	114 (7)	97 (6)	116 (7)
Multiple types of pre-existing CVD	923 (13)	303 (17)	244 (14)	171 (10)	205 (12)
Diabetes mellitus	1210 (17)	389 (22)	323 (18)	247 (14)	251 (14)
Metabolic syndrome	3624 (51)	1066 (60)	906 (51)	828 (47)	824 (47)
Current smoking	1921 (27)	618 (35)	468 (27)	411 (23)	424 (24)
Alcohol consumption	5111 (72)	1118 (63)	1336 (76)	1344 (76)	1313 (75)
Body mass index (kg/m^2)	27.1±4.2	27.7±4.5	27±4.4	26.8±3.9	26.8±3.8
<25 kg/m^2	2274 (32)	481 (27)	576 (33)	613 (35)	604 (34)
25–30 kg/m^2	3313 (47)	800 (45)	837 (47)	832 (47)	844 (48)
>30 kg/m^2	1471 (21)	484 (27)	354 (20)	318 (18)	315 (18)
Systolic blood pressure (mm Hg)	138±20	139±21	138±21	137±19	138±19
Total cholesterol (mmol/L)	4.4 (3.8–5.2)	4.5 (3.8–5.3)	4.4 (3.7–5.1)	4.3 (3.7–5.2)	4.4 (3.8–5.2)
LDL cholesterol (mmol/L)	2.5 (1.9–3.1)	2.5 (1.9–3.1)	2.4 (1.9–3.1)	2.4 (1.9–3.1)	2.5 (2–3.1)
HDL cholesterol (mmol/L)	1.2 (1–1.5)	1.2 (1–1.4)	1.2 (1–1.5)	1.2 (1–1.5)	1.2 (1–1.5)
Antihypertensive medication	5495 (78)	1382 (78)	1367 (77)	1380 (78)	1366 (78)
Lipid-lowering treatment	5501 (78)	1313 (74)	1379 (78)	1433 (81)	1376 (78)

Data are presented as number (%), mean±SD or median (IQR) as appropriate.
AAA, abdominal aortic aneurysm; CAD, coronary artery disease; CeVD, cerebrovascular disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTPA, leisure-time physical activity; METh/wk, metabolic equivalent of task hours per week; PAD, peripheral artery disease.

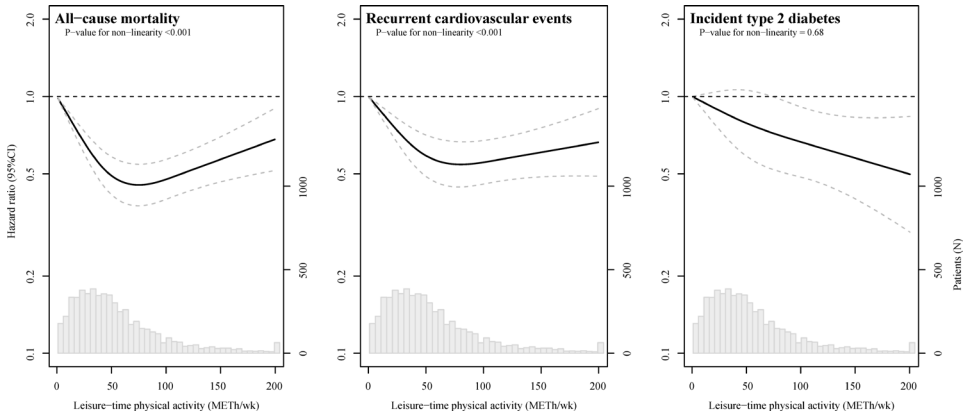

Figure 2 Continuous association between leisure-time physical activity and risk of all-cause mortality, recurrent cardiovascular events and incident type 2 diabetes. Associations between continuous leisure-time physical activity and all-cause mortality (A), recurrent vascular events (B) and incident type 2 diabetes (C). HRs are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and current employment (model 3). The histograms inside the figures represent the number of study participants that achieved a certain leisure-time physical activity level. METh/wk, metabolic equivalent of task hours per week.

Table 2 Association between leisure-time physical activity and all-cause mortality, recurrent cardiovascular events and incident type 2 diabetes

	Leisure-time physical activity level, HR (95% CI)			
	Quarter 1	Quarter 2	Quarter 3	Quarter 4
All-cause mortality				
Events/N total	434/1746	434/1740	255/1732	262/1739
Follow-up (person-years)	15 007	15 392	15 218	15 214
Model 1	Reference	0.66 (0.57 to 0.77)	0.55 (0.47 to 0.65)	0.55 (0.47 to 0.65)
Model 2	Reference	0.73 (0.63 to 0.85)	0.63 (0.54 to 0.73)	0.64 (0.54 to 0.73)
Model 3	Reference	0.73 (0.63 to 0.85)	0.63 (0.54 to 0.74)	0.63 (0.54 to 0.74)
Model 4	Reference	0.74 (0.64 to 0.86)	0.65 (0.55 to 0.76)	0.66 (0.56 to 0.77)
Recurrent vascular events				
Events/N total	342/1746	342/1740	221/1732	244/1739
Follow-up (person-years)	14 023	14 427	14 455	14 356
Model 1	Reference	0.78 (0.67 to 0.91)	0.60 (0.51 to 0.71)	0.65 (0.55 to 0.77)
Model 2	Reference	0.84 (0.72 to 0.99)	0.67 (0.56 to 0.79)	0.72 (0.61 to 0.84)
Model 3	Reference	0.85 (0.72 to 0.99)	0.67 (0.56 to 0.79)	0.72 (0.60 to 0.84)
Model 4	Reference	0.86 (0.74 to 1.01)	0.69 (0.58 to 0.82)	0.74 (0.62 to 0.87)
Type 2 diabetes				
Events/N total	139/1447	139/1445	106/1437	93/1436
Follow-up (person-years)	11 894	12 046	11 815	11 921
Model 1	Reference	0.77 (0.60 to 0.98)	0.76 (0.58 to 0.97)	0.65 (0.50 to 0.84)
Model 2	Reference	0.84 (0.65 to 1.09)	0.85 (0.66 to 1.10)	0.72 (0.55 to 0.94)
Model 3	Reference	0.86 (0.67 to 1.11)	0.86 (0.66 to 1.11)	0.71 (0.55 to 0.93)
Model 4	Reference	0.91 (0.71 to 1.18)	0.96 (0.74 to 1.25)	0.79 (0.61 to 1.04)

Multivariable-adjusted HRs and 95% CIs. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for: smoking, pack years and alcohol use. Model 3 additionally adjusted for education level and current employment. Model 4 was adjusted for model 3 and history of type 2 diabetes, body mass index, systolic blood pressure and low-density lipoprotein cholesterol. Model 3 was used as the main outcome.

Table 3 Association between occupational physical activity and all-cause mortality, recurrent cardiovascular events and incident type 2 diabetes

	Occupational physical activity level, HR (95% CI)			
	Sedentary	Standing	Manual	Heavy manual
All-cause mortality				
Events/N total	540/3558	307/1449	313/1605	94/446
Follow-up (person-years)	29 482	12 713	14 804	3831
Model 1	Reference	1.21 (1.05 to 1.39)	1.07 (0.92 to 1.24)	1.20 (0.97 to 1.50)
Model 2	Reference	1.16 (1.01 to 1.34)	0.99 (0.86 to 1.16)	1.12 (0.90 to 1.40)
Model 3	Reference	1.14 (0.99 to 1.31)	0.98 (0.84 to 1.14)	1.08 (0.86 to 1.35)
Model 4	Reference	1.13 (0.98 to 1.30)	0.97 (0.83 to 1.12)	1.09 (0.87 to 1.36)
Recurrent vascular events				
Events/N total	486/3558	231/1449	284/1605	87/446
Follow-up (person-years)	27 980	11 969	13 806	3506
Model 1	Reference	1.10 (0.94 to 1.29)	1.22 (1.05 to 1.43)	1.34 (1.07 to 1.68)
Model 2	Reference	1.04 (0.89 to 1.22)	1.13 (0.96 to 1.32)	1.21 (0.96 to 1.53)
Model 3	Reference	1.02 (0.87 to 1.20)	1.10 (0.94 to 1.28)	1.15 (0.91 to 1.45)
Model 4	Reference	1.01 (0.86 to 1.18)	1.08 (0.92 to 1.26)	1.15 (0.91 to 1.46)
Type 2 diabetes				
Events/N total	214/2948	87/1163	111/1287	35/367
Follow-up (person-years)	23 514	9747	11 411	3004
Model 1	Reference	1.01 (0.79 to 1.31)	1.14 (0.90 to 1.44)	1.25 (0.87 to 1.79)
Model 2	Reference	0.97 (0.76 to 1.25)	1.06 (0.84 to 1.35)	1.15 (0.81 to 1.66)
Model 3	Reference	0.93 (0.72 to 1.20)	0.98 (0.77 to 1.25)	1.04 (0.72 to 1.50)
Model 4	Reference	0.92 (0.71 to 1.18)	0.97 (0.76 to 1.25)	0.91 (0.63 to 1.32)

Multivariable-adjusted HRs and 95% CIs. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for: smoking, pack years and alcohol use. Model 3 additionally adjusted for education level and current employment. Model 4 was adjusted for model 3 and history of type 2 diabetes, body mass index, systolic blood pressure and low-density lipoprotein cholesterol. Model 3 was used as the primary model.

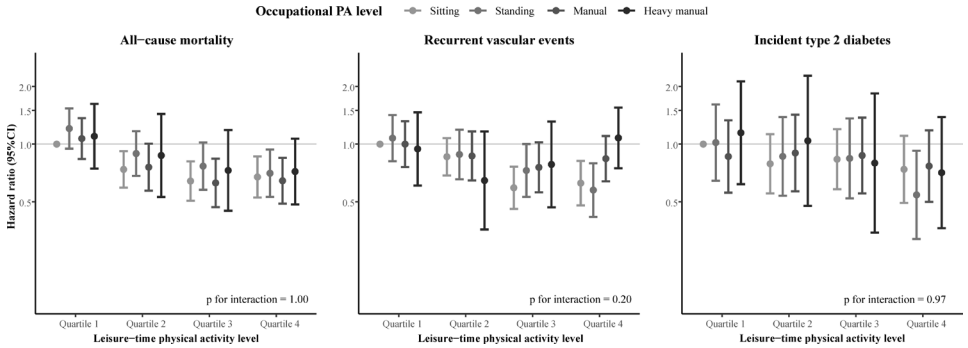

Figure 3 Interaction between leisure-time (LTPA) and occupational physical activity (OPA) on the risk of all-cause mortality recurrent vascular events and incident type 2 diabetes. HRs assessing the interaction between LTPA and OPA level in the association with all-cause mortality, recurrent cardiovascular events and incident type 2 diabetes. These figures show the HRs for each combination of LTPA and OPA level with the least active (quarter 1 LTPA and sedentary OPA) as reference category. Models were adjusted for age, sex, smoking, pack years, alcohol consumption, education and current employment (model 3). Numerical values for the presented HRs are included in online supplemental table 3.

the primary outcomes in never-smokers (eg, incident T2D HR 1.87, 95% CI 1.04 to 3.37 for manual vs sedentary OPA).

In actively employed participants (N=3478), OPA was more strongly associated with detrimental health effects compared with unemployed or retired participants, especially for recurrent vascular events (HR 1.30, 95% CI 1.01 to 1.67 for heavy manual vs sedentary, online supplemental table 5). The harmful health effects of OPA were more pronounced in men (online supplemental table 6A–D).

To address potential reverse causality, sensitivity analyses were performed excluding participants who experienced an outcome within 1, 3 or 5 years after inclusion and the results were similar in size and direction to main analysis (online supplemental figure 4). A complete case analysis resulted in associations that were similar in size and direction to the main analysis (data not shown).

DISCUSSION

In patients with established CVD, higher levels of LTPA were associated with a lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D. In contrast, OPA, especially standing and manual work, was associated with an increased risk of all-cause mortality and recurrent cardiovascular events, notably in men, actively employed participants, patients with a history of CeVD and non-smokers. Furthermore, the beneficial effects of LTPA were attenuated in patients with (heavy) manual work. These findings suggest that the physical activity paradox also manifests in patients with established CVD.

The health benefits of increasing LTPA are widely accepted in healthy populations and supported by multiple prospective cohort studies.[8–10] In patients with established CVD, studies show that people with the highest LTPA level have up to 50% lower risk of all-cause mortality and 35% lower risk of recurrent CVD events, which is in line with the findings in our study.[17 18] In the present study, the association between LTPA and cardiovascular and mortality risk had a reverse J-shape, meaning that a level of LTPA exists beyond which additional activity no longer confers further risk reduction. This finding is in line with previous studies in apparently healthy populations[8] and with findings in two cohorts of patients with CVD.[17 18] Potential explanations for the plateauing and even reversal of the beneficial effects of LTPA at higher levels include atherosclerotic plaque rupture during vigorous exercise or triggering of arrhythmias in scarred myocardial tissue.[22 23]

Interestingly, LTPA was protective of cardiovascular mortality and non-fatal stroke but was associated with an increase in non-fatal MI risk. A potential explanation for these contrasting associations is that LTPA does not reduce the number of events, but prevents events from being fatal by limiting the ischaemic damage incurred to heart muscle. Mechanisms for this process include improved blood flow, vasodilation and angiogenesis in coronary arteries.[24 25] These adaptations could reduce infarct size and infarction-reperfusion injury after a recurrent cardiovascular event.

The associations of LTPA and OPA with T2D have not extensively been studied in CVD populations, but in apparently healthy populations, a linear association with LTPA was observed.[10] Potential explanations for the protective effect of LTPA on T2D include weight loss and increased insulin sensitivity through upregulation of GLUT4 transporters in skeletal muscles.[10 26] In the present study, OPA was not associated with T2D risk. Possible explanations for this lack of effect include that OPA is associated with other lifestyle factors that increase the risk of T2D (eg, unhealthy diet) or that the low-intensity, repetitive character of OPA puts less strain on skeletal muscles and therefore does not result in upregulation of GLUT4.

In apparently healthy populations, higher OPA levels have been associated with up to 50% increased risk of mortality and CVD.[12] In the present study, higher OPA levels were associated with risk increases of approximately 10%, which is in line with previous evidence from exploratory analyses in CVD subgroups.[16] A possible explanation for this difference in effect size could be that UCC-SMART participants with CVD were around retirement age, while OPA conferred stronger harmful effects in a subgroup of actively employed participants. Furthermore, the results could have been affected by index event bias.

Although standing work is commonly thought of as health promoting, this idea might not hold for patients with established CVD.[27] Our results showed that standing OPA was associated with increased risk of all-cause and cardiovascular mortality and non-fatal stroke. The haemodynamic effects of prolonged standing may lead to blood pooling in the extremities, increased pulse pressure and vascular turbulence, ultimately increasing risk of cardiovascular, specifically cerebrovascular, events.[15]

An explanation for the contrasting health effects of LTPA and OPA should be sought in the differing characteristics of the physical activity types.[28] LTPA usually has higher intensity and shorter duration, while OPA requires low-intensity repetitive

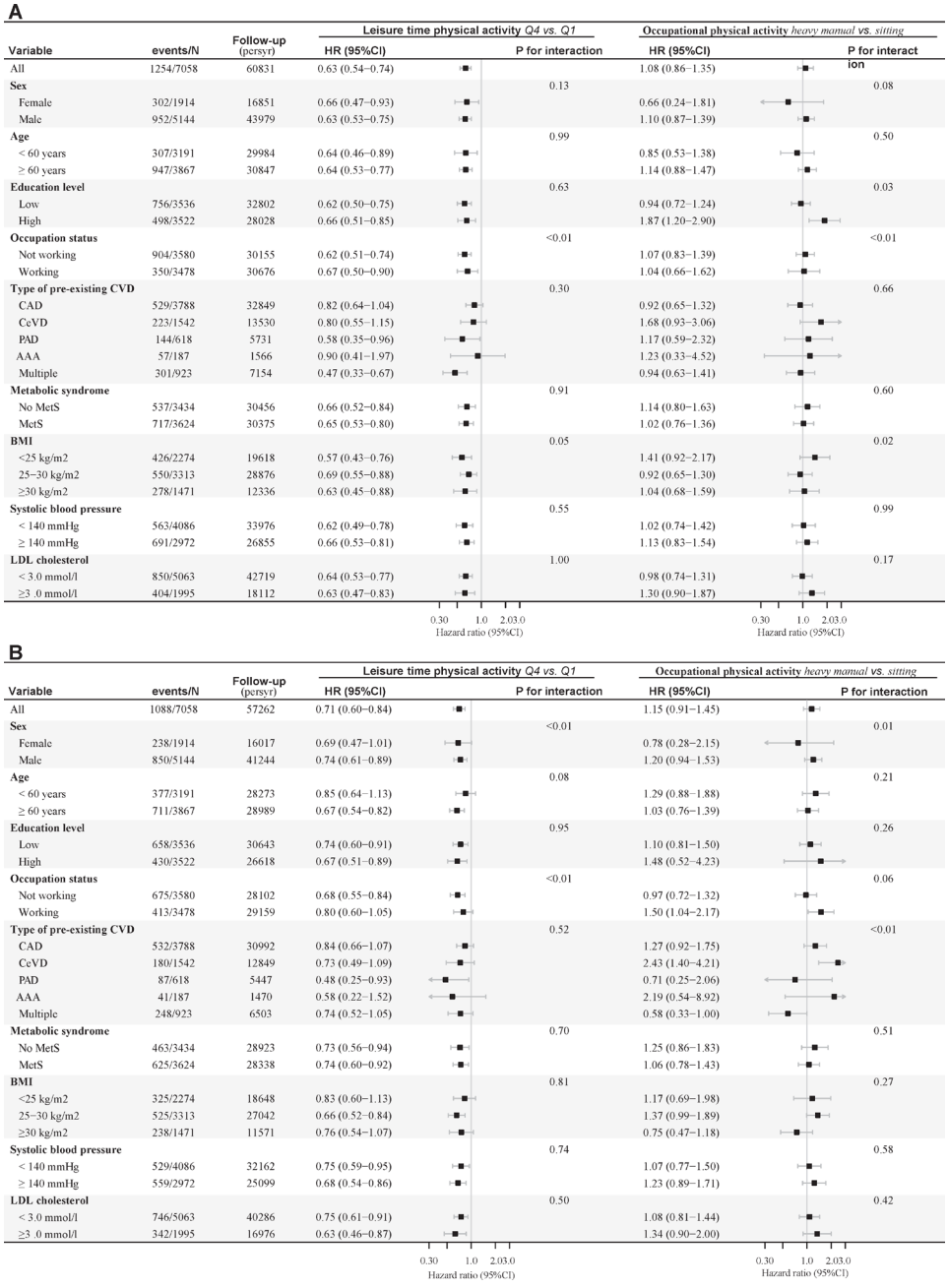

Figure 4 Potential effect modifiers in the association between leisure-time (LTPA) and occupational physical activity (OPA) and clinical endpoints. (A) Effect modification in association with all-cause mortality; (B) effect modification in association with recurrent cardiovascular events. Association between the highest versus lowest quarter of LTPA and heavy manual OPA versus sedentary OPA and all-cause mortality and recurrent cardiovascular events, stratified for potential effect modifiers. HRs are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and active employment (model 3). After Bonferroni correction for multiple testing, a p value of <0.001 (<0.05/36 tests) was considered statistically significant. AAA, abdominal aortic aneurysm; BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; MetS, metabolic syndrome; PAD, peripheral artery disease; persyr, person-years.

movements with short recovery times. Therefore, it has been hypothesised that OPA does not lead to the cardiovascular benefits and improved cardiorespiratory fitness that can be achieved with LTPA and instead has unhealthy effects, such as increased 24-hour heart rate, systolic blood pressure and systemic inflammation.[28]

Another explanation for the finding that OPA does not improve health outcomes might be residual confounding. Manual work is associated with heavier smoking habits and unhealthy diet. Furthermore, people with manual work have has a higher chance of exposure to toxic environmental factors and more frequently do shift work which is independently associated with increased CVD risk.[29] In the current analyses, attempts were made to account for socioeconomic status by adjusting for education level, and the estimated HR decreased slightly toward the null. In studies with more extensive adjustment for socioeconomic factors, the detrimental health effects of OPA were still upheld.[12] In never-smokers, the detrimental associations of OPA were also found, indicating that residual confounding from smoking status did not bias the main findings. Ultimately, it is

difficult to disentangle the effect of OPA itself from the effects of other (lifestyle) factors that often accompany it. Further research is needed to better understand the effects of physically demanding work so specific OPA recommendations can be implemented in guidelines.

Strengths of our study include its size, prospective design, comprehensive data collection and low rate of loss to follow-up. Study limitations include that OPA level was assessed at baseline only, while the majority of the study population was no longer actively employed at that time. This may have diluted the overall effect estimates for OPA, as a sensitivity analysis in actively employed patients yielded stronger associations. Moreover, the physical activity questionnaire was only validated for ranking participants from lowest to highest LTPA level and, therefore, it was impossible to estimate an optimal LTPA level. Furthermore, LTPA and OPA were based on self-reporting, which may lead to optimistic estimates due to social desirability bias. There is, however, no reason to assume the extent of over-reporting differs between low and high levels of LTPA, which means that ranking of individuals will remain unaffected. OPA estimates may have been biased by a healthy workers effect, an important form of selection bias in occupational epidemiology research, because unhealthy people are more likely to switch to less physically demanding occupations.[30] As a result, the associations for the more physically demanding OPA categories could have been biased towards the null.

In conclusion, in patients with established CVD, higher LTPA was associated with a lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D, but this relationship was not observed for higher OPA levels. These findings support the existence of a *physical activity paradox* in patients with established CVD, because they show that while LTPA is beneficial, physically demanding OPA may have harmful effects. Healthcare providers should be aware of these potentially harmful effects of OPA, and OPA should therefore not be regarded as a substitute for LTPA.

Author affiliations
[1]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[2]University Medical Center Utrecht Brain Center, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[3]Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[4]Department of Vascular Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[5]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

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Contributors NEB was responsible for designing the work, performing data analyses, interpreting the results and drafting the manuscript. YR, MJMC, GJdB and AMM were responsible for revising the manuscript. CK was responsible for designing the work, interpreting the results and revising the manuscript. FLJV was responsible for designing the work, interpreting the results and revising the manuscript, and is the manuscript's guarantor.

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ORCID iD
Frank L J Visseren http://orcid.org/0000-0003-3951-5223

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Supplemental material to

Leisure-time and occupational physical activity and health outcomes in cardiovascular disease

Nadia E. Bonekamp, Frank L.J. Visseren, Ynte M. Ruigrok, Maarten-Jan M. Cramer, Gert-Jan de Borst, Anne M. May, Charlotte Koopal on behalf of the UCC-SMART study group

Corresponding author: Frank L.J. Visseren, Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands, F.L.J.Visseren@umcutrecht.nl

Table of contents

Figure S1 – Flowchart UCC-SMART participants selection 3

Table S1 – Baseline characteristics of UCC-SMART participants stratified for OPA 4

Table S2 – Hazard ratios for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality 6

Table S2a – Specific vascular outcomes and LTPA 6

Table S2b – Specific vascular outcomes and OPA 7

Figure S2 - Continuous association between leisure-time physical activity and non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality 8

Figure S3 – Interaction between LTPA and OPA on the risk of all-cause mortality recurrent vascular events, and incident T2D. 9

Table S3 – Hazard ratios for interplay between LTPA and OPA 10

Figure S4 – Associations with start of follow-up after 1, 3 and 5 years after inclusion 11

Table S4 – Hazard ratios for LTPA and OPA in patients that never smoked 12

Table S4a: Hazard ratios for different levels of LTPA in never-smokers. 12

Table S4b: Hazard ratios for different levels of OPA in never-smokers. 13

Table S5 – Hazard ratios for OPA stratified for employment status at inclusion in the UCC-SMART cohort 14

Table S5a: Hazard ratios for OPA among actively employed UCC-SMART participants 14

Table S5b: Hazard ratios for OPA among UCC-SMART participants without active employment 15

Table S6 – Hazard ratios for LTPA and OPA stratified for sex 16

Table S6a: Hazard ratios for LTPA in female UCC-SMART participants 16

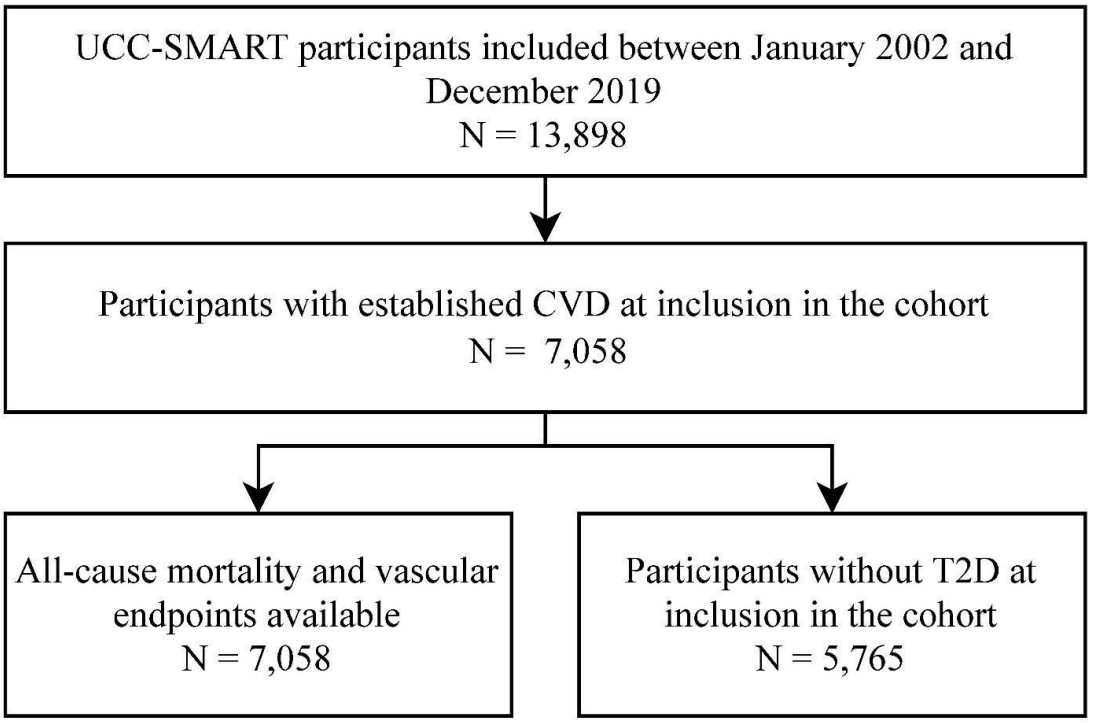
Table S6b: Hazard ratios for OPA in female UCC-SMART participants 16

Table S6c: Hazard ratios for LTPA in male UCC-SMART participants 17

Table S6d: Hazard ratios for OPA in male UCC-SMART participants 17

Bonekamp NE, *et al. Heart* 2022;0:1–9. doi: 10.1136/heartjnl-2022-321474

Figure S1 – Flowchart UCC-SMART participants selection



Legend: Flowchart describing the criteria used to create the datasets used in the analyses of the association between physical activity levels and different outcomes. All datasets were limited to participants included from January 2002 onwards, because a new questionnaire for physical activity level was introduced then. All datasets were limited to participants with established cardiovascular disease at baseline.

Data on all-cause mortality, cause-specific mortality and recurrent cardiovascular events was available for all participants.. The analysis for incident type 2 diabetes was limited to participants without diabetes at baseline.

Table S1 – Baseline characteristics of UCC-SMART participants stratified for OPA

	Not working				Working			
Characteristic	**Sedentary** *N = 1600*	**Standing** *N = 808*	**Manual** *N = 924*	**Heavy manual** *N = 248*	**Sedentary** *N = 1958*	**Standing** *N = 641*	**Manual** *N = 681*	**Heavy manual** *N = 198*
Male sex	1282 (80)	532 (66)	417 (45)	227 (92)	1626 (83)	434 (68)	440 (65)	186 (94)
Age (years)	66 ±9	66 ±9	65 ±9	65 ±9	55 ±9	56 ±9	57 ±9	56 ±10
Leisure-time physical activity								
Quartile 1	405 (25)	206 (26)	247 (27)	72 (29)	509 (26)	139 (22)	147 (22)	40 (20)
Quartile 2	430 (27)	202 (25)	219 (24)	49 (20)	549 (28)	144 (23)	145 (21)	29 (15)
Quartile 3	405 (25)	192 (24)	229 (25)	52 (21)	535 (27)	164 (26)	148 (22)	38 (19)
Quartile 4	360 (23)	208 (26)	229 (25)	75 (30)	365 (19)	194 (30)	241 (35)	91 (46)
Education								
Low	434 (27)	271 (34)	362 (39)	115 (46)	338 (17)	170 (27)	183 (27)	54 (27)
Middle	548 (34)	334 (41)	485 (53)	119 (48)	702 (36)	280 (44)	412 (61)	128 (65)
High	618 (39)	203 (25)	77 (8)	14 (6)	918 (47)	191 (30)	86 (13)	16 (8)
History of CAD	1084 (68)	502 (62)	582 (63)	182 (73)	1253 (64)	402 (63)	400 (59)	146 (74)
History of CeVD	454 (28)	254 (31)	287 (31)	67 (27)	538 (28)	190 (30)	217 (32)	46 (23)
History of PAD	225 (14)	140 (17)	129 (14)	44 (18)	276 (14)	82 (13)	94 (14)	13 (7)
History of AAA	148 (9)	61 (8)	66 (7)	32 (13)	92 (5)	28 (4)	42 (6)	12 (6)
Multiple types of pre-existing CVD	275 (17)	130 (16)	123 (13)	66 (27)	189 (10)	54 (8)	67 (10)	19 (10)
Diabetes mellitus	351 (22)	159 (20)	202 (22)	55 (22)	243 (12)	97 (15)	84 (12)	19 (10)
Metabolic syndrome	835 (52)	404 (50)	547 (59)	155 (63)	920 (47)	320 (50)	335 (49)	108 (55)
Current smoking	333 (21)	193 (24)	240 (26)	78 (32)	543 (28)	217 (34)	245 (36)	72 (36)
Alcohol consumption	1236 (77)	547 (68)	547 (59)	152 (61)	1590 (81)	461 (72)	456 (67)	122 (62)
Body mass index (kg/m2)	26.85 (4)	26.89 (4)	27.34 (4)	28.29 (4)	26.89 (4)	26.93 (4)	27.21 (4)	28.42 (5)
<25 kg/m2	546 (34)	284 (35)	279 (30)	46 (19)	634 (32)	229 (36)	214 (31)	42 (21)
25-30 kg/m2	754 (47)	347 (43)	432 (47)	129 (52)	962 (49)	279 (44)	312 (46)	98 (50)
>30 kg/m2	300 (19)	177 (22)	213 (23)	73 (29)	362 (19)	133 (21)	155 (23)	58 (29)
Systolic blood pressure (mmHg)	139 ±20	142 ±21	143 ±22	140 ±21	134 ±19	136 ±20	138 ±20	135 ±19
LDL cholesterol (mmol/l)	2.4 [1.9-3.0]	2.5 [1.9-3.1]	2.4 [2.0-3.1]	2.5 [1.9-3.1]	2.4 [1.9-3.1]	2.5 [2.0-3.3]	2.6 [2.0-3.2]	2.5 [2.0-3.2]
Antihypertensive medication	1314 (82)	649 (80)	749 (81)	211 (85)	1448 (74)	473 (74)	487 (72)	164 (83)
Lipid-lowering treatment	1252 (78)	618 (77)	727 (79)	209 (84)	1543 (79)	497 (78)	497 (73)	158 (80)

Legend: Data are presented as number (%), mean ±standard deviation or median [interquartile range] as appropriate.Abbreviations: METh/wk: Metabolic equivalent of task hours per week, CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral artery disease, AAA: abdominal aortic aneurysm, LDL: low density lipoprotein, HDL: high density lipoprotein.

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Table S2 – Hazard ratios for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality

Table S2a – Specific vascular outcomes and LTPA

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
Non-fatal myocardial infarction				
Events/N total	325/1,765	322/1,767	345/1,763	357/1,763
Follow-up (persyr)	13,030	13,196	13,013	12,832
Model 1	*Reference*	0.97 (0.83-1.13)	1.03 (0.89-1.20)	1.06 (0.91-1.23)
Model 2	*Reference*	1.00 (0.86-1.17)	1.07 (0.92-1.25)	1.06 (0.91-1.24)
Model 3	*Reference*	1.03 (0.88-1.21)	1.12 (0.96-1.30)	1.12 (0.96-1.30)
Non-fatal stroke				
Events/N total	96/1,765	87/1,767	57/1,763	82/1,763
Follow-up (persyr)	14,592	14,992	14,946	14,912
Model 1	*Reference*	0.87 (0.65-1.16)	0.57 (0.41-0.79)	0.81 (0.60-1.09)
Model 2	*Reference*	0.93 (0.69-1.24)	0.62 (0.44-0.86)	0.87 (0.64-1.17)
Model 3	*Reference*	0.92 (0.69-1.23)	0.61 (0.44-0.86)	0.86 (0.64-1.16)
Cardiovascular mortality				
Events/N total	187/1,765	133/1,767	103/1,763	101/1,763
Follow-up (persyr)	15,007	15,392	15,218	15,214
Model 1	*Reference*	0.68 (0.54-0.84)	0.52 (0.41-0.66)	0.49 (0.38-0.62)
Model 2	*Reference*	0.73 (0.59-0.92)	0.57 (0.45-0.72)	0.54 (0.42-0.69)
Model 3	*Reference*	0.76 (0.61-0.96)	0.61 (0.48-0.78)	0.58 (0.45-0.74)

Legend: Hazard ratios and corresponding 95% confidence intervals for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

Abbreviations: persyr: person year

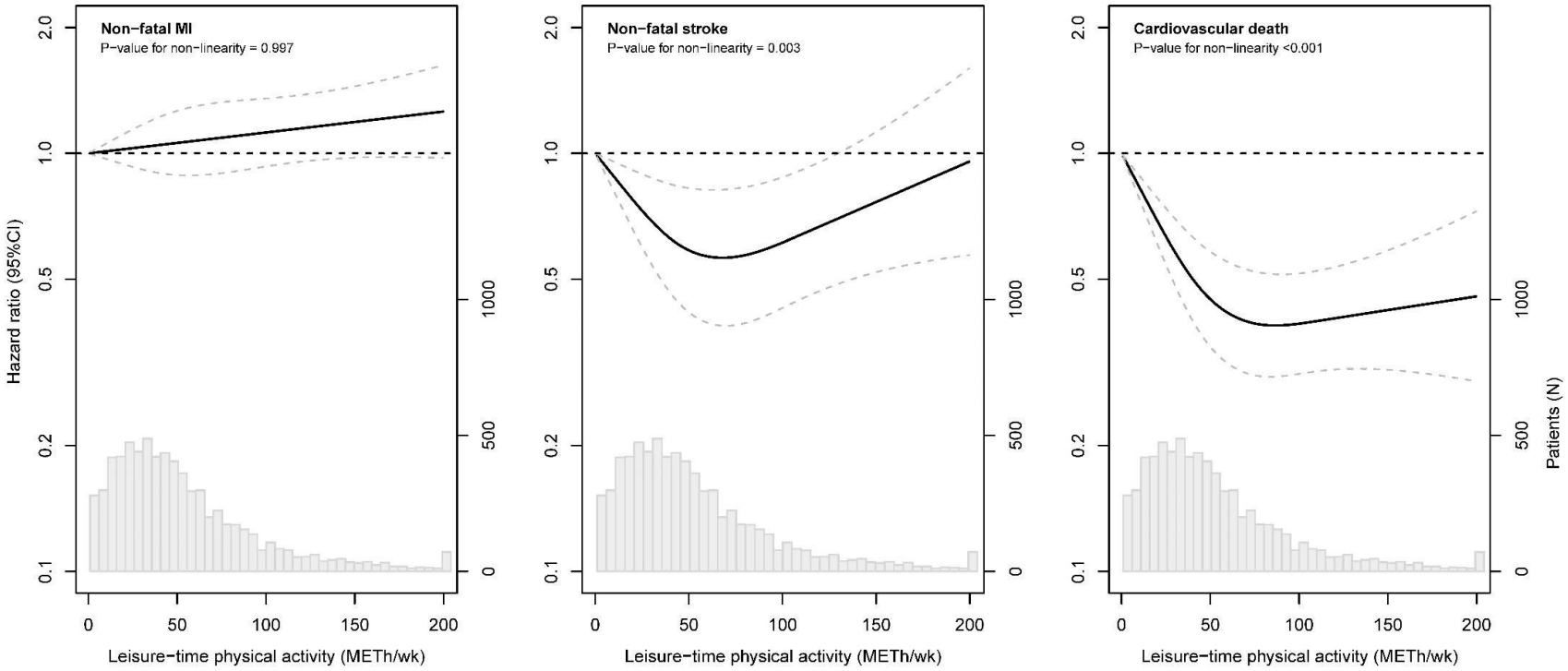
Table S2b – Specific vascular outcomes and OPA

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
Non-fatal myocardial infarction				
Events/N total	662/3,558	258/1,449	321/1,605	108/446
Follow-up (persyr)	25,331	10,994	12,578	3,170
Model 1	*Reference*	0.97 (0.84-1.13)	1.16 (1.01-1.33)	1.22 (0.99-1.49)
Model 2	*Reference*	0.92 (0.80-1.07)	1.06 (0.92-1.22)	1.07 (0.87-1.32)
Model 3	*Reference*	0.92 (0.79-1.06)	1.05 (0.91-1.21)	1.05 (0.85-1.29)
Non-fatal stroke				
Events/N total	127/3,558	74/1449	91/1,605	30/446
Follow-up (persyr)	28,934	12415	14,394	3,699
Model 1	*Reference*	1.31 (0.98-1.75)	1.40 (1.05-1.85)	1.77 (1.19-2.64)
Model 2	*Reference*	1.27 (0.95-1.70)	1.35 (1.01-1.81)	1.66 (1.10-2.50)
Model 3	*Reference*	1.25 (0.93-1.68)	1.34 (1.00-1.79)	1.74 (1.15-2.63)
Cardiovascular mortality				
Events/N total	233/3,558	131/1,449	125/1,605	35/446
Follow-up (persyr)	29,482	12,713	14,804	3,831
Model 1	*Reference*	1.22 (0.98-1.51)	1.04 (0.83-1.31)	1.03 (0.72-1.46)
Model 2	*Reference*	1.14 (0.92-1.42)	0.93 (0.74-1.17)	0.90 (0.62-1.29)
Model 3	*Reference*	1.12 (0.90-1.39)	0.91 (0.72-1.15)	0.89 (0.62-1.28)

Legend: Hazard ratios and corresponding 95% confidence intervals for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

Abbreviations: persyr: person year.

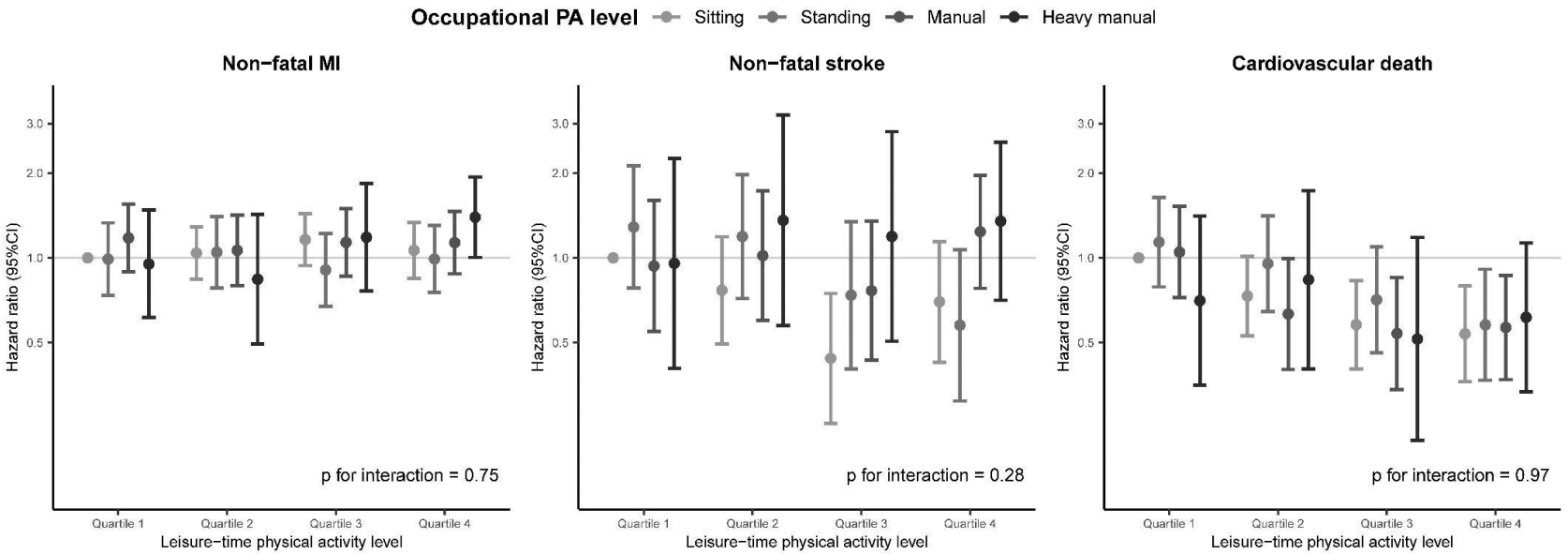
Figure S2 - Continuous association between leisure-time physical activity and non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality



Legend: Hazard ratios are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and current employment (model 3). The histograms inside the figures represent the number of study participants that achieved a certain leisure-time physical activity level.

Abbreviations: METh/wk: Metabolic equivalent of task hours per week. 95%CI: 95% confidence interval

Figure S3 – Interaction between LTPA and OPA on the risk of all-cause mortality recurrent vascular events, and incident T2D.



Legend: Hazard ratios assessing the interaction between LTPA and OPA level in the association with the individual components of the combined vascular endpoint: non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. These figures show the hazard ratios for each combination of leisure-time and OPA level with the least active (quartile 1 leisure-time and sedentary OPA) as reference category. Models were adjusted for age, sex, smoking, packyears, alcohol consumption, education and current employment.

Abbreviations: 95%CI: 95% confidence interval, Mi: myocardial infarction.

Table S3 – Hazard ratios for interplay between LTPA and OPA

Table S3a - All-cause mortality

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.74 (0.59-0.92)	0.64 (0.51-0.81)	0.67 (0.53-0.86)
	Standing	1.21 (0.95-1.54)	0.89 (0.68-1.17)	0.77 (0.58-1.02)	0.70 (0.53-0.94)
	Manual	1.07 (0.84-1.37)	0.76 (0.57-1.01)	0.63 (0.47-0.84)	0.64 (0.49-0.85)
	Heavy manual	1.10 (0.75-1.62)	0.87 (0.53-1.44)	0.73 (0.45-1.18)	0.72 (0.48-1.07)

Table S3b - Recurrent vascular events

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.86 (0.69-1.08)	0.59 (0.46-0.76)	0.63 (0.48-0.82)
	Standing	1.07 (0.81-1.42)	0.88 (0.66-1.19)	0.73 (0.53-1.00)	0.58 (0.42-0.8)
	Manual	1.00 (0.76-1.32)	0.87 (0.65-1.16)	0.76 (0.56-1.02)	0.84 (0.64-1.1)
	Heavy manual	0.94 (0.61-1.47)	0.65 (0.36-1.16)	0.78 (0.47-1.31)	1.08 (0.75-1.55)

Table S3c - Incident type 2 diabetes

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.79 (0.55-1.13)	0.83 (0.58-1.20)	0.74 (0.49-1.11)
	Standing	1.02 (0.64-1.61)	0.86 (0.54-1.38)	0.84 (0.52-1.36)	0.54 (0.32-0.92)
	Manual	0.86 (0.56-1.33)	0.90 (0.57-1.42)	0.87 (0.55-1.38)	0.77 (0.50-1.18)
	Heavy manual	1.15 (0.62-2.13)	1.04 (0.48-2.28)	0.80 (0.35-1.84)	0.71 (0.36-1.38)

Legend: Hazard ratios assessing the interaction between LTPA and OPA level in the association with all-cause mortality, recurrent vascular events and incident type 2 diabetes. All presented hazard ratios are relative to people with sedentary OPA and LTPA quarter 1. Models were adjusted for age, sex, smoking, pack years, alcohol consumption, education and current employment.

Abbreviations: 95%CI: 95% confidence interval, HR: hazard ratio

Figure S4 – Associations with start of follow-up after 1, 3 and 5 years after inclusion.

Outcome	Start Follow-up	Events/N	Follow−up (pers.yr)	LTPA Q4 *vs.*Q1	Hazard ratio (95%CI)	OPA Heavy manual vs sedentary	Hazard ratio (95%CI)
Mortality	All	1254/7058	60831		0.61 (0.52−0.71)		1.09 (0.87−1.37)
	1 year	1199/6702	60629		0.61 (0.52−0.72)		1.11 (0.89−1.40)
	3 year	1040/5957	59105		0.63 (0.53−0.74)		1.09 (0.85−1.40)
	5 year	847/5136	55813		0.62 (0.52−0.75)		1.10 (0.83−1.45)
Combined vascular endpoint	All	1088/7058	57262		0.71 (0.60−0.83)		1.16 (0.92−1.47)
	1 year	952/6599	57019		0.68 (0.57−0.82)		1.09 (0.84−1.41)
	3 year	775/5759	55327		0.69 (0.57−0.84)		1.02 (0.76−1.37)
	5 year	600/4870	51763		0.71 (0.57−0.89)		0.97 (0.69−1.36)
Diabetes	All	447/5765	47676		0.68 (0.52−0.89)		1.04 (0.72−1.50)
	1 year	423/5460	47507		0.69 (0.52−0.90)		1.09 (0.75−1.58)
	3 year	312/4782	46114		0.71 (0.52−0.97)		1.12 (0.73−1.72)
	5 year	219/4045	43164		0.64 (0.43−0.95)		1.09 (0.65−1.85)

Legend: Hazard ratios for all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes with the full dataset and with datasets that exclude participants with an event in the first 1, 3 or 5 years after inclusion. The presented estimates were adjusted for the covariates included in model 3. These figures show the hazard ratio for the highest quartile *vs.* these lowest quartile of leisure-time physical activity and the highest level of occupational physical activity (heavy manual work) *vs.* sedentary.

Abbreviations: FU: follow-up, pers.yr: person year, 95%CI: 95% confidence interval, LTPA: leisure-time physical activity, OPA: Occupational physical activity.

Bonekamp NE, *et al. Heart* 2022;0:1–9. doi: 10.1136/heartjnl-2022-321474

Table S4 – Hazard ratios for LTPA and OPA in patients that never smoked

Table S4a: Hazard ratios for different levels of LTPA in never-smokers.

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Events/N total	64/374	50/426	33/441	44/447
Follow-up (persyr)	2910	3620	3675	3783
Model 1	*Reference*	0.66 (0.45-0.96)	0.48 (0.31-0.74)	0.55 (0.37-0.81)
Model 2	*Reference*	0.66 (0.45-0.96)	0.50 (0.33-0.77)	0.56 (0.38-0.83)
Model 3	*Reference*	0.72 (0.49-1.05)	0.55 (0.36-0.85)	0.66 (0.44-0.98)
Combined vascular endpoint				
Events/N total	57/374	50/426	29/441	50/447
Follow-up (persyr)	2722	3453	3550	3596
Model 1	*Reference*	0.71 (0.49-1.04)	0.42 (0.27-0.66)	0.68 (0.46-0.99)
Model 2	*Reference*	0.74 (0.50-1.08)	0.45 (0.29-0.71)	0.45 (0.29-0.71)
Model 3	*Reference*	0.77 (0.52-1.13)	0.47 (0.30-0.75)	0.46 (0.28-0.73)
Type 2 diabetes				
Events/N total	24/363	15/408	21/434	19/442
Follow-up (persyr)	2428	2847	2969	3084
Model 1	*Reference*	0.54 (0.28-1.04)	0.73 (0.40-1.31)	0.62 (0.34-1.14)
Model 2	*Reference*	0.62 (0.32-1.19)	0.83 (0.46-1.52)	0.67 (0.36-1.23)
Model 3	*Reference*	0.66 (0.34-1.29)	0.94 (0.51-1.72)	0.80 (0.43-1.48)

Legend: Sensitivity analysis limited to SMART participants that reported they had never smoked (N = 1688). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

***** The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.

Abbreviations: persyr: person year.

Table S4b: Hazard ratios for different levels of OPA in never-smokers.

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	73/869	40/329	63/393	15/97
Follow-up (persyr)	6661	2942	3486	898
Model 1	*Reference*	0.98 (0.66-1.45)	1.24 (0.84-1.82)	1.01 (0.58-1.76)
Model 2	*Reference*	0.97 (0.65-1.44)	1.27 (0.85-1.89)	1.04 (0.58-1.86)
Model 3	*Reference*	0.93 (0.62-1.38)	1.26 (0.84-1.87)	1.03 (0.58-1.86)
Combined vascular endpoint				
Events/N total	73/869	39/329	58/393	16/97
Follow-up (persyr)	6408	2789	3279	845
Model 1	*Reference*	1.10 (0.74-1.64)	1.31 (0.89-1.93)	1.44 (0.83-2.47)
Model 2	*Reference*	1.02 (0.68-1.52)	1.20 (0.81-1.79)	1.20 (0.81-1.79)
Model 3	*Reference*	0.99 (0.66-1.48)	1.18 (0.79-1.77)	1.26 (0.72-2.21)
Type 2 diabetes				
Events/N total	32/752	11/271	30/306	6/84
Follow-up (persyr)	5603	2400	2579	744
Model 1	*Reference*	0.77 (0.38-1.55)	1.94 (1.11-3.37)	1.29 (0.53-3.09)
Model 2	*Reference*	0.76 (0.37-1.54)	1.87 (1.04-3.37)	1.17 (0.47-2.92)
Model 3	*Reference*	0.74 (0.36-1.50)	1.85 (1.01-3.36)	1.04 (0.41-2.58)

Legend: Sensitivity analysis limited to SMART participants that reported they had never smoked (N = 1688). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

* The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.

Abbreviations: persyr: person year.

Table S5 – Hazard ratios for OPA stratified for employment status at inclusion in the UCC-SMART cohort

Table S5a: Hazard ratios for OPA among actively employed UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	166/1958	77/641	84/681	23/198
Follow-up (persyr)	16696	5811	6425	1744
Model 1	*Reference*	1.22 (0.93-1.61)	1.09 (0.83-1.43)	1.13 (0.73-1.74)
Model 2	*Reference*	1.13 (0.86-1.49)	0.95 (0.72-1.26)	1.04 (0.66-1.62)
Model 3	*Reference*	1.11 (0.84-1.46)	0.98 (0.74-1.29)	1.13 (0.72-1.77)
Combined vascular endpoint				
Events/N total	198/1958	73/641	106/681	36/198
Follow-up (persyr)	15987	5563	6021	1588
Model 1	Reference	1.12 (0.85-1.47)	1.50 (1.18-1.90)	1.65 (1.15-2.35)
Model 2	Reference	1.03 (0.79-1.36)	1.30 (1.01-1.67)	1.30 (1.01-1.67)
Model 3	Reference	1.01 (0.77-1.33)	1.29 (1.01-1.66)	1.54 (1.06-2.23)
Type 2 diabetes				
Events/N total	127/1704	43/539	45/591	18/174
Follow-up (persyr)	13861	4620	5396	1445
Model 1	*Reference*	1.09 (0.77-1.55)	0.97 (0.69-1.37)	1.26 (0.77-2.07)
Model 2	*Reference*	0.99 (0.70-1.41)	0.81 (0.57-1.16)	1.13 (0.68-1.89)
Model 3	*Reference*	0.98 (0.69-1.40)	0.84 (0.59-1.21)	1.01 (0.61-1.69)

Legend: Sensitivity analysis limited to SMART participants that reported they had active employment at the moment of inclusion in the cohort (n = 3,478). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

* The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.

Abbreviations: persyr: person year

Table S5b: Hazard ratios for OPA among UCC-SMART participants without active employment

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	374/1600	230/808	229/924	71/248
Follow-up (persyr)	12786	6902	8380	2087
Model 1	*Reference*	1.17 (0.99-1.38)	1.04 (0.87-1.24)	1.19 (0.92-1.53)
Model 2	*Reference*	1.14 (0.96-1.34)	0.98 (0.82-1.17)	1.07 (0.83-1.39)
Model 3	*Reference*	1.13 (0.95-1.33)	0.97 (0.81-1.15)	1.07 (0.83-1.39)
Combined vascular endpoint				
Events/N total	288/1600	158/808	178/924	51/248
Follow-up (persyr)	11993	6405	7786	1918
Model 1	*Reference*	1.05 (0.87-1.28)	1.03 (0.85-1.26)	1.13 (0.84-1.53)
Model 2	*Reference*	1.01 (0.83-1.22)	0.96 (0.78-1.18)	0.96 (0.78-1.18)
Model 3	*Reference*	1.00 (0.82-1.22)	0.95 (0.78-1.17)	0.98 (0.72-1.34)
Type 2 diabetes				
Events/N total	87/1244	44/624	66/696	17/193
Follow-up (persyr)	9653	5127	6015	1559
Model 1	*Reference*	0.96 (0.67-1.39)	1.24 (0.88-1.73)	1.20 (0.71-2.01)
Model 2	*Reference*	0.91 (0.63-1.31)	1.11 (0.79-1.56)	1.00 (0.59-1.69)
Model 3	*Reference*	0.88 (0.61-1.28)	1.06 (0.75-1.50)	0.85 (0.50-1.45)

Legend: Sensitivity analysis limited to SMART participants that reported they were not actively employed at the moment of inclusion in the cohort (n = 3,580). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

* The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.

Abbreviations: persyr: person year

Table S6 – Hazard ratios for LTPA and OPA stratified for sex

Table S6a: Hazard ratios for LTPA in female UCC-SMART participants

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Model 1	*Reference*	0.56 (0.42-0.75)	0.49 (0.36-0.67)	0.48 (0.34-0.67)
Model 2	*Reference*	0.59 (0.44-0.79)	0.51 (0.37-0.70)	0.54 (0.39-0.75)
Model 3	*Reference*	0.61 (0.45-0.82)	0.55 (0.40-0.75)	0.57 (0.41-0.80)
Combined vascular endpoint				
Model 1	*Reference*	0.67 (0.48-0.93)	0.57 (0.40-0.81)	0.54 (0.37-0.78)
Model 2	*Reference*	0.68 (0.49-0.94)	0.60 (0.42-0.86)	0.58 (0.40-0.84)
Model 3	*Reference*	0.73 (0.53-1.02)	0.68 (0.47-0.97)	0.64 (0.44-0.93)
Type 2 diabetes				
Model 1	*Reference*	0.74 (0.44-1.26)	1.06 (0.65-1.72)	0.82 (0.47-1.42)
Model 2	*Reference*	0.76 (0.45-1.28)	1.08 (0.66-1.77)	0.83 (0.48-1.43)
Model 3	*Reference*	0.83 (0.49-1.41)	1.18 (0.72-1.92)	0.91 (0.52-1.58)

Table S6b: Hazard ratios for OPA in female UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Model 1	*Reference*	1.35 (0.98-1.86)	1.54 (1.16-2.05)	1.11 (0.41-3.04)
Model 2	*Reference*	1.16 (0.84-1.61)	1.10 (0.82-1.47)	0.78 (0.28-2.14)
Model 3	*Reference*	1.11 (0.80-1.54)	1.03 (0.76-1.38)	0.71 (0.26-1.94)
Combined vascular endpoint				
Model 1	*Reference*	1.19 (0.83-1.71)	1.44 (1.05-1.96)	1.32 (0.48-3.63)
Model 2	*Reference*	1.07 (0.74-1.53)	1.07 (0.78-1.47)	1.01 (0.37-2.78)
Model 3	*Reference*	0.98 (0.69-1.41)	0.92 (0.66-1.27)	0.83 (0.30-2.29)
Type 2 diabetes				
Model 1	*Reference*	0.68 (0.38-1.20)	1.29 (0.84-1.97)	1.71 (0.53-5.57)
Model 2	*Reference*	0.65 (0.37-1.15)	1.17 (0.76-1.82)	1.58 (0.48-5.15)
Model 3	*Reference*	0.60 (0.34-1.06)	0.98 (0.63-1.53)	1.17 (0.36-3.86)

Table S6c: Hazard ratios for LTPA in male UCC-SMART participants

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Model 1	*Reference*	0.72 (0.60-0.85)	0.60 (0.51-0.72)	0.62 (0.52-0.74)
Model 2	*Reference*	0.68 (0.58-0.81)	0.57 (0.47-0.68)	0.56 (0.47-0.66)
Model 3	*Reference*	0.70 (0.59-0.83)	0.58 (0.48-0.69)	0.56 (0.47-0.66)
Combined vascular endpoint				
Model 1	*Reference*	0.84 (0.70-1.00)	0.63 (0.52-0.77)	0.72 (0.60-0.87)
Model 2	*Reference*	0.82 (0.68-0.98)	0.61 (0.51-0.74)	0.69 (0.57-0.83)
Model 3	*Reference*	0.85 (0.71-1.01)	0.63 (0.52-0.77)	0.69 (0.58-0.83)
Type 2 diabetes				
Model 1	*Reference*	0.77 (0.58-1.02)	0.67 (0.50-0.90)	0.60 (0.45-0.81)
Model 2	*Reference*	0.77 (0.58-1.02)	0.67 (0.50-0.90)	0.60 (0.45-0.82)
Model 3	*Reference*	0.81 (0.61-1.08)	0.70 (0.52-0.95)	0.61 (0.45-0.82)

Table S6d: Hazard ratios for OPA in male UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Model 1	*Reference*	1.37 (1.17-1.61)	1.04 (0.87-1.25)	1.29 (1.03-1.62)
Model 2	*Reference*	1.22 (1.04-1.43)	1.05 (0.87-1.25)	1.23 (0.98-1.54)
Model 3	*Reference*	1.17 (0.99-1.37)	0.97 (0.80-1.16)	1.11 (0.88-1.39)
Combined vascular endpoint				
Model 1	*Reference*	1.17 (0.98-1.40)	1.26 (1.05-1.50)	1.37 (1.09-1.74)
Model 2	*Reference*	1.01 (0.92-1.32)	1.25 (1.04-1.49)	1.36 (1.08-1.72)
Model 3	*Reference*	1.05 (0.88-1.26)	1.15 (0.96-1.39)	1.20 (0.94-1.53)
Type 2 diabetes				
Model 1	*Reference*	1.17 (0.89-1.54)	1.03 (0.77-1.38)	1.22 (0.84-1.78)
Model 2	*Reference*	1.18 (0.89-1.56)	1.03 (0.77-1.38)	1.22 (0.84-1.78)
Model 3	*Reference*	1.11 (0.84-1.47)	0.91 (0.67-1.23)	1.05 (0.71-1.55)

Legend: Sensitivity analyses stratified for sex. These tables shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.

***** The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.