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Physical exercise volume, type, and intensity and risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease: a mediation analysis

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Aims To estimate the relation between physical exercise volume, type, and intensity with all-cause mortality and recurrent vascular events in patients with cardiovascular disease (CVD) and to quantify to what extent traditional cardiovascular risk factors mediate these relations.

Methods and results In the prospective UCC-SMART cohort ($N = 8660$), the associations of clinical endpoints and physical exercise volume (metabolic equivalent of task hours per week, METh/wk), type (endurance vs. endurance + resistance), and intensity (moderate vs. vigorous) were estimated using multivariable-adjusted Cox models. The proportion mediated effect (PME) through body mass index, systolic blood pressure, low-density lipoprotein cholesterol, insulin sensitivity, and systemic inflammation was assessed using structural equation models. Sixty-one percent of patients (73% male, age 61 ± 10 years, >70% receiving lipid-lowering and blood pressure–lowering medications) reported that they did not exercise. Over a median follow-up of 9.5 years [interquartile range (IQR) 5.1–14.0], 2256 deaths and 1828 recurrent vascular events occurred. The association between exercise volume had a reverse J-shape with a nadir at 29 (95% CI 24–29) METh/wk, corresponding with a HR 0.56 (95% CI 0.48–0.64) for all-cause mortality and HR 0.63 (95% CI 0.55–0.73) for recurrent vascular events compared with no exercise. Up to 38% (95% CI 24–61) of the association was mediated through the assessed risk factors of which insulin sensitivity (PME up to 12%, 95% CI 5–25) and systemic inflammation (PME up to 18%, 95% CI 9–37) were the most important.

Conclusion Regular physical exercise is significantly related with reduced risks of all-cause mortality and recurrent vascular events in patients with CVD. In this population with high rates of lipid-lowering and blood pressure–lowering medication use, exercise benefits were mainly mediated through systemic inflammation and insulin resistance.

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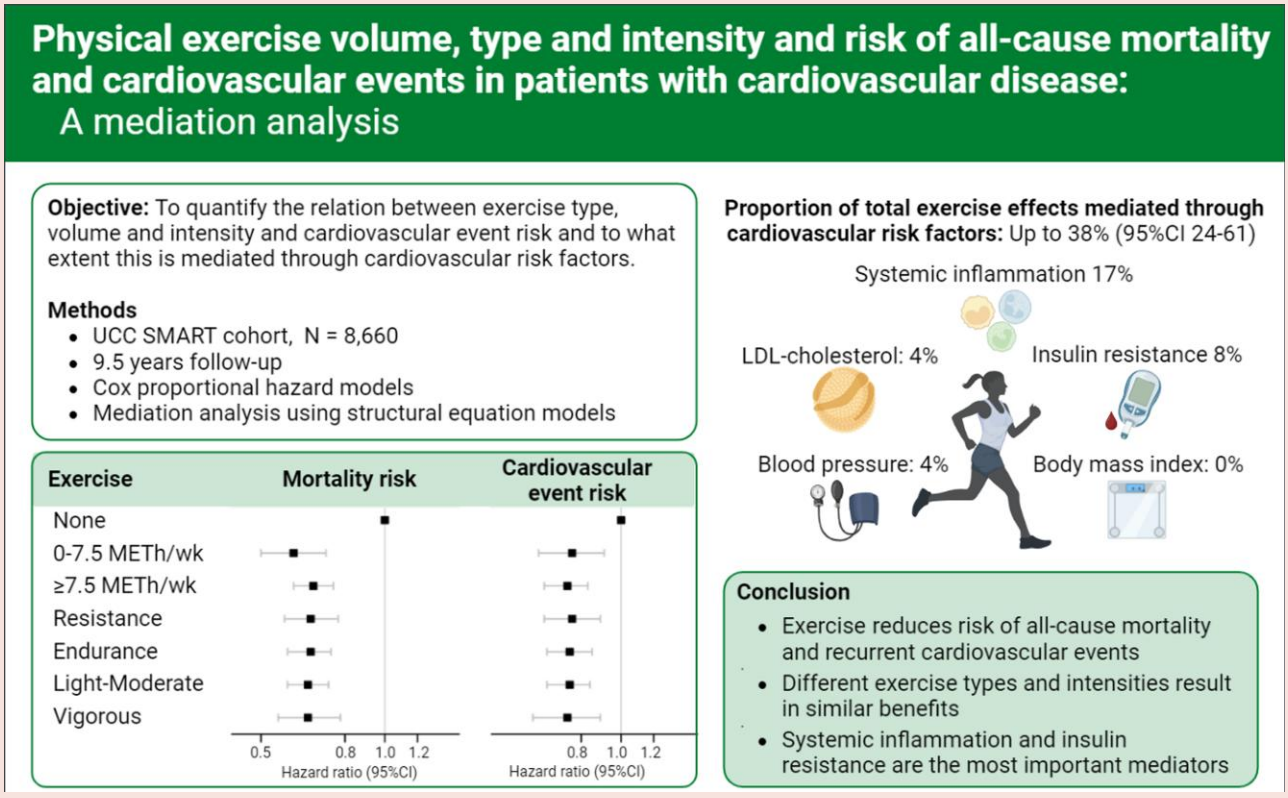
Lay summary

- People that have previously experienced cardiovascular events, like a heart attack or stroke, are at lower risk of a recurrent event or mortality when they regularly perform physical exercise because exercise beneficially affects cardiovascular risk factors.
- Time spent on exercise is the most important determinant of exercise benefits; similar cardiovascular benefits can be achieved with different exercise types and intensities. It is important to choose an exercise modality that suits personal preferences and abilities, as any level of exercise is better than no exercise.
- In the context of well-treated CVD patients, exercise benefits come about through beneficial modification of cardiovascular risk factors, most importantly inflammation and insulin sensitivity.

Graphical Abstract



Keywords Physical exercise • Cardiovascular disease • Resistance training • Endurance training • Low-grade inflammation • Mediation analysis

Introduction

Physical exercise is a key component of a healthy lifestyle and has consistently been associated with reduced rates of all-cause mortality and cardiovascular disease (CVD).[1–3] Performing regular exercise is a central recommendation in international guidelines for CVD management, which distinguish between exercise type, e.g. resistance or endurance training, and intensity.[4,5] Resistance training predominantly has musculoskeletal benefits and reduces risk of CVD and some types of cancer; it is specifically recommended for improving physical functioning and glycaemic control.[6–8] Endurance exercise effectively improves cardiorespiratory fitness, reduces subcutaneous fat mass, and lowers CVD risk.[9,10] However, the optimal exercise volume, type, and intensity are unknown for patients with CVD.[11]

Exercise has been shown to attenuate traditional CVD risk factors,[12–15] reduce systemic inflammation,[16,17] increase insulin sensitivity,[18,19] and improve cardiorespiratory fitness.[20] However, the relative contributions of these mediating pathways are unclear and it is unknown if mediators differ across exercise types and intensities. Better understanding of the causal pathway between exercise and cardiovascular events may help inform patients with CVD about the most beneficial way to exercise.

We aimed to quantify the relation between exercise volume, type, and intensity and risk of all-cause mortality and recurrent vascular events in patients with a history of CVD. Furthermore, we aimed to quantify to which extent the effects of exercise are mediated through body mass index (BMI), insulin resistance, systemic inflammation, systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDL-C).

Methods

Study population

The Utrecht Cardiovascular Cohort—Second Manifestations of ARTerial disease (UCC-SMART) study is a single-centre prospective cohort study that comprises patients at high risk of or with established CVD. Details on study design have been published previously.[21] The local Medical Ethics Review Committee approved the study, and all participants gave written informed consent.

For the present study, data were used from 8660 participants with established CVD at inclusion in the cohort. Participants were included between 1996 and 2019, and history of CVD was defined as either coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm (see Supplementary material online, *Figure S1*).

Baseline measurements and determination of exercise volume, intensity, and type

All participants completed a baseline health questionnaire and underwent a physical examination and laboratory testing. Physical activity was self-reported and assessed using the validated EPIC physical activity questionnaire with additional questions on type and duration of exercise.[22] The EPIC questionnaire showed moderate–high agreement with 3-day activity diaries especially in men (Spearman correlation coefficients between 0.32 and 0.81).[22] Detailed information on exercise was available, i.e. the exact sports activity that a participant participated in and the number of hours spent on that activity each week. Metabolic equivalent of task (MET) values for the reported exercise activities were calculated according to the Compendium of Physical Activity.[23] Exercise is commonly defined as a planned, structured, and goal-oriented activity, which best translates to sport-related physical activity in the UCC-SMART study.[24] For this analysis, exercise was assessed in three ways: exercise volume, exercise type, and exercise intensity.

(1) Exercise volume was defined as the average intensity of exercise (the MET value) times weekly hours spent on exercise and was measured in METh/wk. It was analysed both continuously and categorically in three groups: (i) no exercise, (ii) > 0 and <7.5 METh/wk, and (iii) ≥ 7.5 METh/wk. This 7.5 METh/wk cut-off was based on guideline-recommended exercise volume and corresponds to 150 min/week of moderate-intensity exercise or 75 min/week of vigorous exercise.[4,5]
(2) Exercise intensity was based on the MET value of the exercise and was assessed categorically in three groups: (i) no exercise, (ii) light–moderate-intensity exercise with a MET value between 0 and 6, and, (iii) vigorous intensity with a MET value ≥6.
(3) Exercise type was determined by classifying the reported exercise activity as either (i) no exercise, (ii) resistance training, or (iii) combined endurance–resistance training, based on the classification proposed by the Dutch National Institute of Public Health and the Environment.[25]

Outcome measurement

The primary outcomes were all-cause mortality and recurrent vascular events, a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality. These components were assessed as secondary outcomes. Outcomes were assessed in biannual follow-up questionnaires and requesting additional information from the treating physician for all reported events. Three independent physicians made the final endpoint adjudication based on pre-published definitions.[21]

Statistical analysis

Baseline characteristics were presented as frequencies with percentages for categorical variables and as means with standard deviation or median with interquartile range (IQR) for continuous variables. Cox proportional hazard models with time-on study as the time scale were used to estimate the relations of exercise volume, intensity, and type with the outcomes. Model 1 adjusted for age and sex. Model 2, the main model, additionally adjusted for smoking status, pack years, alcohol consumption, and education level. Model 3 further adjusted for covariates that could be either intermediates or confounders: SBP, LDL-C, type 2 diabetes (T2D), and BMI. To model the association with exercise volume as a continuous variable, Cox models with restricted cubic splines with three knots were selected based on Akaike information criterion (AIC). The nadir exercise volume and corresponding 95% confidence intervals (95% CIs) were obtained in 1000 bootstrap samples.

Mediation analysis was performed with marginal structural models in a counterfactual framework.[26–28] Potential mediators were selected based on previous etiologic research: BMI, SBP, systemic inflammation, insulin resistance, and LDL-C (*Figure 1*). To ensure stability of the models, the exposure was dichotomized and mediators were categorized into sex-specific quintiles. A weighted Cox regression model was used to estimate the total, direct and indirect effect, and the proportion mediated effect (PME). The 95% CIs for these estimates were obtained in 1000 bootstrap samples. A detailed methodology is provided in see Supplementary material online, *Supplemental appendix 1*.

The mediation analysis was repeated in subgroups based on sex, metabolic syndrome (MetS), and a low-grade inflammatory state (defined as CRP level between 2 and 10 mg/L). In a subgroup of people without type

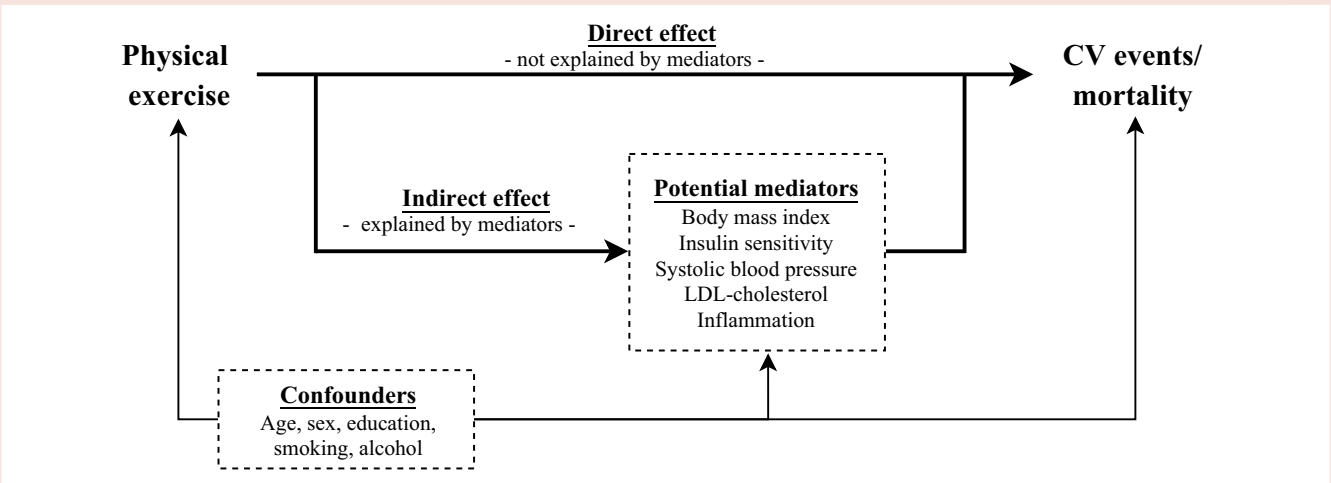


Figure 1 Path diagram of the relation between physical exercise and cardiovascular events and all-cause mortality. Legend: Causal path diagram of the relation between physical exercise and cardiovascular events and all-cause mortality. CV, cardiovascular; LDL, low-density lipoprotein.

2 diabetes, the mediation analysis was repeated using HOMA-IR for insulin resistance. To check robustness of the total effect estimates from these mediation analyses, subgroup analyses were repeated using traditional Cox proportion hazard models adjusted for age, sex, education, smoking, number of pack years, and alcohol consumption. To assess independence of the mediating pathways, PMEs were estimated in models including one mediator at a time. To assess the impact of reverse confounding, the analyses were repeated in subsets with follow-up commencing after 1, 3, and 5 year after inclusion.

Missing data on education (22.7%), SBP (0.1%), smoking status and pack years (0.1%), alcohol consumption (0.3%), BMI (0.1%), serum triglycerides (0.1%), and C-reactive protein (2.3%) were imputed with single imputation using predictive mean matching. All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 8660 patients with established CVD were included. Mean age was 61 ± 10 years and 73% were men. Over 70% of the cohort was treated with lipid-lowering and blood pressure–lowering medications. The majority (61%) of participants reported that they did not exercise (*Table 1*). Compared with these non-exercisers, people who exercised more frequently had higher levels of education (38% vs. 19%), were less frequently smokers (20% vs. 36%), and less frequently had T2D (12% vs. 20%).

Baseline characteristics were similar for resistance and endurance exercise (*Table 1*). Participants who engaged in vigorous intensity exercise were younger (58 vs. 60 years) and more frequently male (78% vs. 74%) compared with those who engaged in light–moderate intensity (*Table 1*). Moreover, T2D and MetS were less prevalent among vigorous exercisers (7% vs. 14% and 39% vs. 46%, respectively).

Exercise volume

Compared with no exercise, any exercise volume (>0 METh/wk) was related with risk reductions for all-cause mortality and recurrent events. Reverse J-shaped relations were observed for both outcomes, with nadir exercise volume at 29 METh/wk (95% CI 24–90) which related with HR 0.56 (95% CI 0.48–0.64) for all-cause mortality and HR 0.63 (95% CI 0.55–0.73) for recurrent vascular events (Figure 2). The relation with recurrent vascular events was driven by reductions in cardiovascular mortality and non-fatal stroke risk, while no relation with non-fatal myocardial infarction was found (see Supplementary material online, *Figure S2*). Compared with no exercise, exercise volumes >0 and ≤7.5 METh/wk were related with HR 0.67 (95% CI 0.50–0.72) for all-cause mortality and HR 0.76 (95% CI 0.63–0.91) for recurrent events and >7.5 METh/wk with HR 0.68 (95% CI 0.61–0.76) and HR 0.73 (95% CI 0.64–0.82), respectively (*Table 2*).

Together, BMI, insulin resistance, SBP, systemic inflammation, and LDL-C mediated 29% (95% CI 21–42) of the relation between exercise volume and all-cause mortality and 32% (95% CI 22–48) for recurrent cardiovascular events. Systemic inflammation and insulin resistance were the most important mediators for both endpoints. Inflammation accounted for 16% (95% CI 12–24) of the relation with all-cause mortality and 17% (95% CI 11–26) with recurrent vascular events, and insulin resistance accounted for 5% (95% CI 2–9) and 8% (95% CI 5–14), respectively.

Exercise type

Compared with non-exercisers, resistance exercise had a lower risk of all-cause mortality, HR 0.66 (95% CI 0.57–0.77), and recurrent vascular events, HR 0.76 (95% CI 0.65–0.89). Combined endurance–resistance activities were similarly related to lower risk for all-cause mortality (HR 0.66, 95% CI 0.58–0.74) and recurrent vascular events (HR 0.75, 95% CI 0.66–0.85, *Table 3*). These relations were driven by reduced risk of cardiovascular mortality and non-fatal stroke (see Supplementary material online, *Table S2*).

The five mediators accounted for 21% (95% CI 14.2–33.9) of the relation between resistance training and all-cause mortality and 27% (95% CI 13.9–61.0) of the relation with recurrent vascular events (*Table 3*). Systemic inflammation was the most important mediator, with PMEs 11% (95% CI 7–20) and 14% (95% CI 9–34), respectively. Insulin resistance mediated 5% (95% CI 2–9) of the relation with all-cause mortality and 9% (95% CI 4–21) of the relation with recurrent vascular events.

For combined endurance–resistance exercise, the total PMEs were 27% (95% CI 20–42) and 38% (95% CI 24–61) for all-cause mortality and recurrent vascular events, respectively. Insulin resistance and inflammation were the most important mediators. Compared with resistance exercise, LDL-C was a more important mediator, accounting for PME 4% (95% CI 2–7) and PME 5% (95% CI 2–11), respectively.

Exercise intensity

Compared with non-exercisers, light–moderate exercise was related to lower risk of all-cause mortality, HR 0.65 (95% CI 0.58–0.73), and recurrent vascular events, HR 0.75 (95% CI 0.66–0.84). These relations were similar for vigorous exercise, HR 0.65 (95% CI 0.55–0.78) and HR 0.74 (95% CI 0.61–0.89), respectively (*Table 2*).

The five mediators accounted for 24% (95% CI 18–34) of the relation between light–moderate exercise and all-cause mortality and 33% (95% CI 26–51) with recurrent vascular (*Table 3*). For vigorous exercise, total PMEs of 31% (95% CI 20–54) for all-cause mortality and 36% for recurrent events were observed (see Supplementary material online, *Table S5*). For both intensities, systemic inflammation was the most important mediator, but the PME for insulin resistance was higher for vigorous exercise than light–moderate exercise: 8% (95% CI 4–16) vs. 3% (95% CI 1–6) for all-cause mortality.

Subgroup and sensitivity analyses

Subgroup analyses

The effects of exercise volume, type, and intensity were similar for men and women (all *P*-values for interaction >0.40, Supplementary material online, *Table S3*). The total PME through the included mediators was lower in females (e.g. 23% for vigorous exercise and all-cause mortality vs. 31% in the full analysis). Specifically, the PME for systemic inflammation was smaller in females, while a larger PME was found for insulin resistance (see Supplementary material online, *Table S3*).

In patients with low-grade inflammation ($N = 3557$), the protective effect of exercise volume, type, and intensity with all-cause mortality and recurrent events was smaller compared with that of the main analysis (*P* for interaction <0.01, Supplementary material online, *Table S3*). A smaller PME through inflammation was observed, e.g. a total PME of 7% (95% CI −2; 12%) in the association between exercise volume and all-cause mortality vs. a PME of 29% (95% CI 21–42) in the main analysis.

In patients with MetS ($n = 4547$), the total PME was lower, e.g. the total PME for exercise volume and recurrent vascular events was 19% (95% CI 5–34) compared with 32% (95% CI 21–51) in the main analysis mainly due to a lower PME through insulin resistance (see Supplementary material online, *Table S3*). Across subgroups with differing BMI, the associations of exercise volume, type, and intensity with all-cause mortality and recurrent cardiovascular events were stronger in people with BMI <25 kg/m^2 or ≥30 kg/m^2 (all *P*-values for interaction <0.02, see Supplementary material online, *Tables S3e-g*). Body mass index remained an unimportant mediator in these subgroups. In patients without T2D, the HOMA-IR formula was used instead of the triglyceride–glucose ratio and findings were similar to the primary analysis (see

Table 1 Baseline characteristics stratified for exercise volume, type, and intensity

		Exercise volume		Exercise type		Exercise intensity[a]	
	No exercise *N = 5266*	>0–7.5 METh/wk *N = 724*	>7.5 METh/wk *N = 2670*	Resistance *N = 1020*	Resistance–endurance *N = 2374*	Light to moderate *N = 2470*	Vigorous *N = 897*
Male (%)	3830 (73)	449 (62)	2097 (79)	732 (72)	1814 (76)	1828 (74)	701 (78)
Age, years	61.2 ± 10	59.8 ± 10	59.4 ± 10	60.9 ± 10	58.9 ± 10	60 ± 10	58 ± 10
Education level (%)							
Low	1816 (35)	201 (28)	557 (21)	231 (23)	527 (22)	559 (23)	192 (21)
Middle	2460 (47)	309 (43)	1033 (39)	425 (42)	917 (38)	1002 (41)	330 (37)
High	990 (19)	214 (30)	1080 (40)	364 (36)	930 (39)	909 (37)	375 (42)
Total leisure time PA, METh/wk	26 (10–51)	30 (16–49)	55 (36–83)	52 (31–84)	49 (3–75)	48 (30–75)	56 (36–84)
Sports-related PA, METh/wk	*NA*	5 (4–6)	18 (12–28)	14 (8–25)	15 (9–24)	13 (8–22)	21 (14–32)
History of CAD (%)	3120 (59)	460 (64)	1748 (66)	689 (68)	1519 (64)	1611 (65)	580 (65)
History of CeVD (%)	1599 (30)	220 (30)	741 (28)	283 (28)	678 (29)	719 (29)	239 (27)
History of PAD (%)	1091 (21)	69 (13)	325 (12)	123 (12)	298 (13)	300 (12)	111 (12)
History of AAA (%)	502 (10)	51 (7)	160 (6)	69 (7)	142 (6)	153 (6)	55 (6)
Multiple CVD manifestations (%)	917 (17)	92 (13)	273 (10)	125 (12)	240 (10)	285 (12)	75 (8)
Type 2 diabetes (%)	1058 (20)	99 (14)	318 (12)	117 (12)	300 (13)	346 (14)	66 (7)
Metabolic syndrome (%)	3037 (58)	357 (49)	1153 (43)	475 (47)	1035 (44)	1143 (46)	353 (39)
Smoking (%)							
Never	992 (19)	195 (27)	763 (29)	325 (32)	633 (27)	680 (28)	273 (30)
Former	2376 (45)	342 (47)	1383 (52)	519 (51)	1206 (51)	518 (21)	183 (20)
Current	1898 (36)	187 (26)	524 (20)	176 (17)	535 (23)	1272 (52)	441 (49)
Body mass index (%)							
<25 kg/m^2	1681 (32)	256 (35)	958 (36)	345 (34)	633 (27)	857 (35)	344 (38)
25–30 kg/m^2	2453 (47)	338 (47)	1304 (49)	495 (49)	535 (23)	1196 (48)	437 (49)
≥ 30 kg/m^2	1132 (22)	130 (18)	408 (15)	180 (18)	1206 (51)	417 (17)	116 (19)
Systolic BP, mmHg	140 ± 21	137 ± 20	137 ± 19	138 ± 20	136 ± 19	137 ± 20	136 ± 19
Diastolic BP, mmHg	81 ± 11	80 ± 11	81 ± 11	80 ± 12	81 ± 11	81 ± 11	81 ± 10
Total cholesterol, mmol/L	4.7 (4.0–5.6)	4.6 (3.9–5.5)	4.5 (3.8–5.3)	4.6 (3.9–5.4)	4.5 (3.8–5.3)	4.5 (3.8–5.4)	4.5 (3.8–5.3)
LDL cholesterol, mmol/L	2.7 (2.1–3.5)	2.6 (2–3.4)	2.5 (2.0–3.3)	2.6 (2.0–3.3)	2.5 (2.0–3.3)	2.5 (2.0–3.3)	2.5 (2.0–3.2)
HDL cholesterol, mmol/L	1.2 (1.0–1.4)	1.2 (1–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)
eGFR[b], mL/min/1.73 m^2	77 (64–89)	78 (66–91)	81 (69–91)	79 (66–98)	81 (69–92)	79 (67–91)	82 (70–93)
CRP, mg/L	2.4 (1.1–5.0)	1.8 (0.8–4.0)	1.6 (0.8–3.3)	1.8 (0.8–3.9)	1.6 (0.8–3.3)	1.7 (0.8–3.5)	1.5 (0.8–3.2)
Antihypertensive medication (%)	3963 (75)	540 (75)	2003 (75)	783 (77)	1760 (74)	1881 (76)	644 (72)
Lipid-lowering medication (%)	3517 (67)	500 (69)	2002 (75)	753 (74)	1749 (74)	1821 (74)	665 (74)

Data are presented as *n* (%) for categorical variables and as means ± standard deviation or median (interquartile range) for continuous variables.
AAA, aortic abdominal aneurysm; BP, blood pressure; CAD, coronary artery disease; CeVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; METh/wk, metabolic equivalent of task hours per week; PA, physical activity; PAD, peripheral artery disease.
[a]For 27 participants, no MET value was available for the sports activity they reported. These participants were excluded from this analysis.
[b]eGFR was estimated using the CKD-EPI formula.

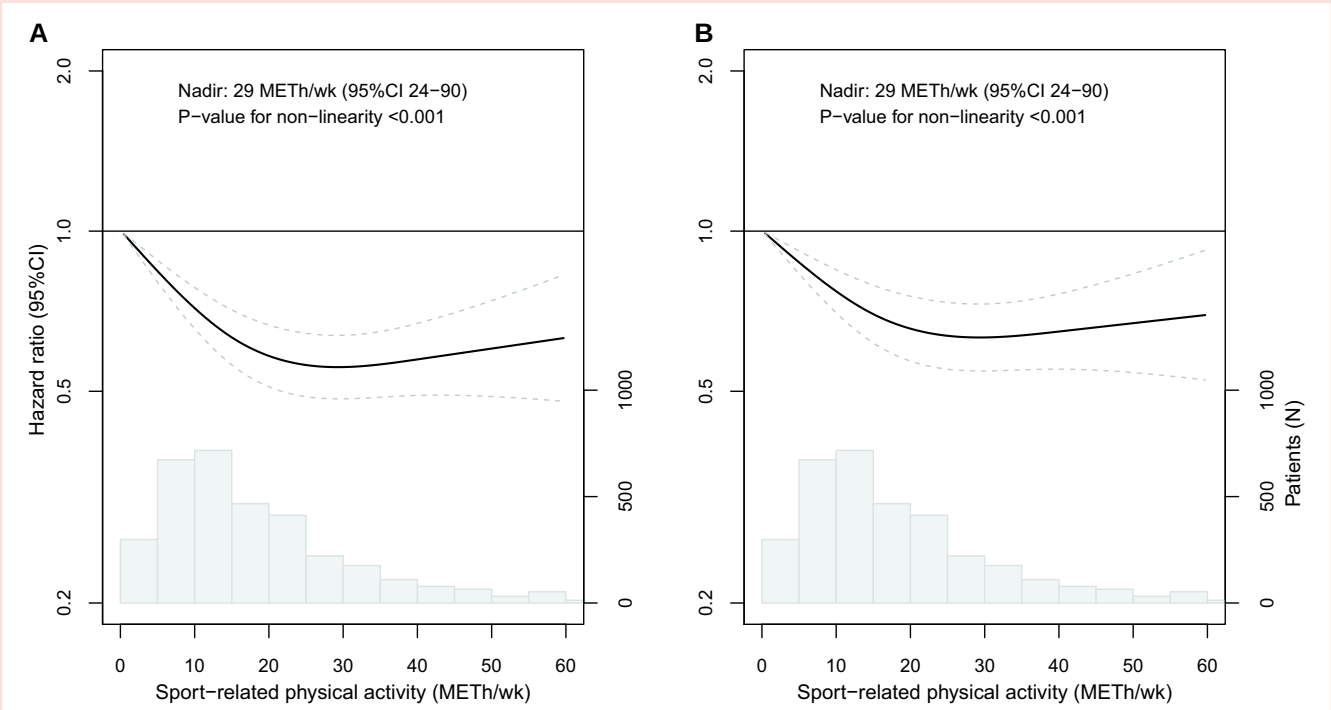


Figure 2 Continuous relation between exercise volume and all-cause mortality and recurrent vascular events. Legend: This figure shows the best fitting restricted cubic splines (with three knots at the 10th, 50th and 90th percentile) for the continuous association between sports-related physical activity level and risk of all-cause mortality (*A*) and recurrent vascular events (*B*). The nadir and corresponding 95% CI for sports-related physical activity are provided in the plots. All splines are adjusted for age, sex, smoking status, number of pack years, alcohol consumption, and education. The histograms in the plots show the number of participants at a specific physical activity level. Non-exercisers ($N = 5266$) are not included in the histogram. METh/wk, metabolic equivalent of task hours per week.

Supplementary material online, *Table S3h*). In a sensitivity analysis, using traditional Cox regression to estimate the relationship between exercise volume, type, and intensity across these subgroups, HRs were comparable with the main analyses (see Supplementary material online, *Table S4a/b*).

Sensitivity analyses

When the mediators were assessed individually to assess independence of the causal paths, a similar PME was found compared with the main analysis (see Supplementary material online, *Table S1*). In analyses excluding patients that experienced an event in the first 1, 3, and 5 years after inclusion, the exercise volume, type, and intensity relations were similar in direction to the main analysis, but the HRs were slightly closer to 1 (see Supplementary material online, *Figure S5A–C*).

Discussion

This study shows that the majority of patients with established CVD report that they do not regularly perform physical exercise. Moreover, we show that exercise is strongly related with reduced risk of recurrent cardiovascular events and all-cause mortality in patients with established CVD, even at a low volume. The associations are reverse J-shaped, with a nadir at 29 METh/wk. METh/wk captures both exercise quantity and intensity, and therefore, more METh/wk can be achieved through either a longer time doing mild intensity exercise or a short time spent on vigorous intensity exercise. The present study found similar relations for different exercise types (muscle strengthening vs. endurance) and intensities (light–moderate vs. vigorous). Over a third of the relations was mediated through changes in BMI, insulin resistance, SBP, systemic inflammation, and LDL-C. Systemic inflammation was the most important mediator and accounted for over 15% of the total effect.

Few long-term studies on exercise have been performed in patients with established CVD, but the available studies report similar risk reductions.[2,3,29,30] One previous study in coronary artery disease patients also found a reverse J-shaped association with mortality risk that plateaued around 20 METh/wk.[29]

In general population studies, muscle strengthening activities have been associated with reductions in risk of mortality and cardiovascular events compared with no exercise, albeit not as strongly as the associations found in the present study.[31] Endurance and resistance training have previously been directly compared in clinical trials, in populations at high CVD risk.[9,32,33] Some found that endurance exercise was more effective in lowering BMI and subcutaneous fat mass than resistance training, but overall, resistance exercise and endurance exercise were similarly beneficial for CVD risk factors.[9,32,33] We add to this existing literature that, in patients with established CVD, there is no great difference in the associations of different exercise types and intensities. Moreover, to our knowledge, we are the first to quantify the contribution of different mediating factors of physical exercise benefits in patients with CVD.

Multiple studies have investigated the physiological effects of exercise, but the relative contributions of these mediators in the association with clinical endpoints remain unknown. For the first time, our study identifies systemic inflammation and insulin resistance as the main mediators for cardiovascular risk reduction with exercise.

Exercise results in the release of anti-inflammatory myokines and adipokines.[34,35] Myokine release is stronger in vigorous and endurance exercise, which could explain why inflammation was a more important

Table 2 Relation between exercise volume, type, and intensity with risk of all-cause mortality and recurrent vascular events

Model	No exercise	Exercise volume HR (95% CI)		Exercise type HR (95% CI)		Exercise intensity HR (95% CI)[a]	
		>0–7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance–endurance	Light to moderate	Vigorous
All-cause mortality							
Events (*n*)	1725	134	397	187	344	386	133
Follow-up (persyr)	52 855	7298	24 252	9587	21 963	22 853	8426
Crude	*Reference*	0.52 (0.43–0.63)	0.52 (0.47–0.58)	0.61 (0.53–0.71)	0.49 (0.44–0.55)	0.54 (0.48–0.6)	0.49 (0.41–0.58)
Model 1	*Reference*	0.56 (0.47–0.68)	0.58 (0.52–0.65)	0.59 (0.51–0.69)	0.59 (0.52–0.66)	0.58 (0.52–0.65)	0.58 (0.49–0.69)
Model 2	*Reference*	0.60 (0.50–0.72)	0.67 (0.60–0.75)	0.66 (0.57–0.77)	0.66 (0.58–0.74)	0.65 (0.58–0.73)	0.65 (0.55–0.78)
Model 3	*Reference*	0.62 (0.51–0.74)	0.68 (0.61–0.77)	0.69 (0.59–0.80)	0.67 (0.59–0.75)	0.66 (0.59–0.74)	0.69 (0.58–0.83)
Recurrent vascular events							
Events (*n*)	1329	128	371	166	333	363	126
Follow-up (persyr)	48 756	6740	22 791	9033	20 499	21 339	7938
Crude	*Reference*	0.66 (0.55–0.79)	0.61 (0.54–0.68)	0.68 (0.58–0.80)	0.60 (0.54–0.68)	0.63 (0.56–0.71)	0.58 (0.49–0.7)
Model 1	*Reference*	0.70 (0.58–0.84)	0.64 (0.57–0.72)	0.67 (0.57–0.79)	0.66 (0.58–0.74)	0.66 (0.59–0.74)	0.64 (0.53–0.77)
Model 2	*Reference*	0.76 (0.63–0.91)	0.74 (0.65–0.83)	0.76 (0.65–0.89)	0.75 (0.66–0.85)	0.75 (0.66–0.84)	0.74 (0.61–0.89)
Model 3	*Reference*	0.78 (0.64–0.94)	0.76 (0.67–0.85)	0.79 (0.67–0.93)	0.77 (0.68–0.87)	0.76 (0.68–0.86)	0.78 (0.65–0.94)

Hazard ratios for guideline-compliant exercise volume, different exercise types, and exercise intensities, compared with people that do not exercise. Model 1 adjusted for age and sex. Model 2 adjusted for model 1 and smoking status, pack years, alcohol consumption, and education level. Model 3 adjusted for model 2 and SBP, LDL cholesterol, type 2 diabetes, and BMI. HR, hazard ratio; 95% CI, 95% confidence interval.

[a]For 27 participants, no MET value was available for the sports activity they reported. These participants were excluded from this analysis.

mediator in these associations. In our study, the beneficial effects of exercise on mortality and recurrent event risk through reduced inflammation were attenuated in patients with low-grade inflammation, possibly because the underlying cause for the low-grade inflammation negates the effects of exercise.

Exercise-induced release of adipokines, like IL-6 and adiponectin, accelerates lipolysis, inhibits gluconeogenesis, and increases insulin sensitivity.[34,36,37] Moreover, exercise stimulates GLUT-4 expression, which results in increased glucose uptake during exercise and improved glycogen storage in rest.[38]

Although the mediators included in this analysis explain about a quarter to a third of the associations with exercise, the lion's share remains unexplained. Previous research has indicated that the benefits of physical exercise exceed the effect that could be expected based on resulting changes in traditional cardiovascular risk factors alone.[39] A potential alternative mediator is cardiorespiratory fitness, which is a strong independent predictor of CVD and all-cause mortality.[40] Additionally, regular exercise induces angioneogenesis and vasodilatation and reduces endothelial dysfunction, ultimately leading to better oxygen delivery.[20,39,41] Theoretically, part of the relation between exercise and health outcomes could also be effectuated through placebo effect. For some patients with established CVD, exercise constitutes an active intervention targeted at reducing health risks and as such it is subject to placebo effect.[42] Placebo effect has been shown to significantly and beneficially affect functional and quality of life measures and may reduce (cardiovascular) event risk.[42,43] Furthermore, in patients with a history of CVD, it has been hypothesized that exercise increases atherosclerotic plaque stability and improves vascular function and coronary circulation, thus limiting ischaemic damage from a next vascular event.[44–46] This is a potential explanation for our findings that higher exercise intensity primarily reduces the mortality rate and has little effects on non-fatal myocardial infarction.

Our study shows that clinically relevant reductions in all-cause mortality and cardiovascular event risk can be achieved through compliance with international exercise guidelines for CVD management. Generally, the observed benefits were similar across exercise types and intensities. We recommend that healthcare professionals focus on motivating their patients to perform any type of exercise that is in line with their capabilities and personal preferences. We identified some subgroups in which the relations of exercise and clinical outcomes were weaker (e.g. patients with MetS or low-grade inflammation), possibly because underlying conditions negate exercise effects mediated through inflammation and insulin sensitivity. However, in these subgroups, a protective association of exercise volume, type, and intensity was still found, and therefore, it remains important to motivate these patients to exercise.

Strengths and limitations

Strengths of the current study include its large sample size, prospective data collection, endpoint adjudication based on medical records, and low rate of loss to follow-up. Study limitations include the need for categorization of exposure and mediator variables and unavailability of data on other potential mediators. Exercise type was not directly assessed in the baseline questionnaire, but approximated based on national guidelines, possibly resulting in misclassification. Moreover, exercise was self-reported, and this should be taken into account when interpreting the results of this study. Although the EPIC physical activity questionnaire was validated against 3-day activity diaries, it was not validated for measuring absolute values of exercise volume. It is however possible to use the results to rank people based on their physical activity. Furthermore, the effect estimates found in this study were similar to those found in studies based on accelerometer-measured exercise levels.[2] The analyses on exercise type were not subject to this limitation, as detailed information on exercise type was available, and this was classified based on standards specifically designed for the Dutch population.[25]

Residual confounding is an important limitation in lifestyle-related research and may arise from difficult-to-measure confounders like social–economic status, frailty, or diet. The majority of the study population

Table 3 Mediation analysis of the effects of exercise volume, type, and intensity

		Exercise volume		Exercise type		Exercise intensity[a]	
		PME (95% CI)		PME (95% CI)		PME (95% CI)	
	No exercise	>0–7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance–endurance	Light to moderate	Vigorous
All-cause mortality							
Total effect, HR (95% CI)	*Reference*	0.59 (0.52–0.66)	0.68 (0.61–0.76)	0.64 (0.54–0.72)	0.64 (0.58–0.72)	0.63 (0.57–0.69)	0.65 (0.55–0.80)
Direct effect, HR (95% CI)	*Reference*	0.64 (0.56–0.69)	0.76 (0.68–0.85)	0.70 (0.61–0.79)	0.72 (0.65–0.82)	0.70 (0.64–0.78)	0.75 (0.62–0.90)
Indirect effect, HR (95% CI)	*Reference*	0.92 (0.91–0.96)	0.89 (0.87–0.92)	0.91 (0.86–0.93)	0.88 (0.86–0.91)	0.89 (0.86–0.92)	0.88 (0.83–0.92)
Total PME (%)		14.8 (8.2–16.9)	28.5 (20.7–42)	21.4 (14.2–33.9)	27.4 (20.4–42.1)	24.0 (17.7–33.9)	31.1 (20.4–54.1)
Mediated through:							
Body mass index (%)		−0.4 (−1.8–0.9)	0.7 (−1.6–3.3)	1.0 (−1.5–4.4)	−0.2 (−2.4–2.1)	0.7 (−1.0–2.3)	−0.5 (−4.6–4.1)
Insulin resistance (%)		2.7 (1.1–5.5)	5.0 (2.1–8.8)	5.2 (2.1–8.7)	4.2 (1.9–7.1)	3.3 (1.0–5.5)	8.2 (3.8–16.3)
Systolic blood pressure (%)		1.8 (−0.9–3.7)	3.1 (1.3–3.8–5.8)	2.3 (0.3–4.5)	3.1 (1.2–5.9)	3.0 (1.3–5.8)	1.9 (−0.6–5.1)
Inflammation (%)		8.7 (2.1–10.1)	16.4 (11.4–24.7)	11.4 (6.8–20.0)	16.5 (12.3–24.2)	14.5 (10.4–19.6)	16.7 (10.7–28.0)
LDL cholesterol (%)		2.1 (0.7–3.7)	3.3 (1.2–6)	1.5 (−0.9–4.8)	3.8 (2.0–7.4)	2.5 (1.0–5.2)	4.8 (1.7–10.7)
Recurrent vascular events							
Total effect, HR (95%CI)	*Reference*	0.72 (0.65–0.86)	0.73 (0.64–0.82)	0.72 (0.62–0.85)	0.72 (0.63–0.79)	0.72 (0.65–0.80)	0.71 (0.59–0.86)
Direct effect, HR (95%CI)	*Reference*	0.78 (0.69–0.92)	0.80 (0.72–0.90)	0.79 (0.70–0.93)	0.82 (0.71–0.91)	0.80 (0.73–0.90)	0.81 (0.65–0.95)
Indirect effect, HR (95%CI)	*Reference*	0.92 (0.91–0.96)	0.90 (0.88–0.92)	0.91 (0.88–0.94)	0.88 (0.85–0.91)	0.90 (0.87–0.92)	0.88 (0.85–0.92)
Total PME		24.2 (10.9–48.7)	32.0 (21.1–50.9)	27.0 (19.3–61.0)	37.9 (23.9–60.8)	33.0 (25.6–51.3)	36.3 (19.6–68.2)
Mediated through:							
Body mass index (%)		−0.2 (−3.5–1.6)	−0.5 (−2.9–1.2)	−0.1 (−2.6–2.9)	−0.4 (−3.0–1.9)	0.1 (−2.1–1.3)	−1.5 (−7.1–2.2)
Insulin resistance (%)		6.7 (3.4–13.7)	8.0 (4.8–13.5)	8.8 (4.4–20.9)	8.3 (4.6–13.7)	7.2 (3.7–11.7)	12.2 (5.1–25.1)
Systolic blood pressure (%)		2.5 (−1.3–9.9)	3.6 (1.4–8.0)	3.2 (0.3–7.7)	4.5 (1.5–9.9)	4.2 (1.8–8.6)	2.7 (−0.4–6.9)
Inflammation (%)		12.1 (1.8–28.1)	17.1 (10.6–26.1)	13.7 (8.6–34.2)	20.2 (13.4–32.6)	18.2 (12.8–28.6)	18.0 (9.4–36.7)
LDL cholesterol (%)		3.2 (1.8–6)	3.7 (1.6–8.0)	1.4 (−1.3–6.1)	5.3 (2.4–11.3)	3.4 (1.4–8.5)	4.9 (1.4–12.4)

Mediation analysis of the associations between exercise volume, type, and intensity and all-cause mortality and recurrent vascular events. Total effect represents the full size of the association between the exposure and the health outcomes. The direct effect is the effect of the exposure that is effectuated through other paths than the included mediators. The indirect effect represents the effect size that is brought about through exercise-related changes in the included mediators. The PME indicates the proportion of the overall effect that is mediated through the included mediators. All models are adjusted for age, sex, smoking status, pack years, alcohol consumption, and education level.
95% CI, 95% confidence interval; HR, hazard ratio; LDL, low-density lipoprotein; METh/wk, metabolic equivalent of task hours per week; PME, proportion mediated effect.
[a]For 27 participants, no MET value was available for the sports activity they reported. These participants were excluded from this analysis.

was treated with blood pressure–lowering and lipid-lowering therapy, which may partly explain the small PMEs through SBP and LDL cholesterol. Evidence suggests that in patients using lipid-lowering therapies, the LDL cholesterol lowering effects of exercise are smaller,[13] while add-on blood pressure–lowering effects are still observed for patients using blood pressure–lowering drugs.[12] Blood pressure–lowering and lipid-lowering pharmacological therapies are standard of care in patients with established CVD, but caution is warranted in applying the current study's findings to populations without blood pressure and LDL cholesterol medication. Mediation analysis with structural equation models assumes independence of the included causal pathway, which is difficult to assess. However, in a sensitivity analysis assessing mediators independently, the PME was similar compared with the main analysis. Finally, exercise and mediator levels were measured at the same time. This cross-sectional assessment means that it is impossible to establish the direction of the causal effect. However, the included mediators were selected because previous intervention studies showed that exercise influenced them (and not the other way around).

Conclusions

Physical exercise is associated with a reduced risk of all-cause mortality and recurrent vascular events in patients with established CVD. When counselling CVD patients on lifestyle optimization, they should be advised to perform physical exercise in a manner that fits with their person abilities and preferences. Any level of exercise is associated with clinically relevant reduction in mortality and CVD risk reductions, and health benefits are similar across different exercise types and intensities. In the context of standard pharmacological CVD prevention, up to a third of the effect of exercise is mediated through improvement in traditional cardiovascular risk factors, of which systemic inflammation and insulin resistance are the most important. In populations with lower usage of lipid-lowering and blood pressure–lowering medications, other factors may play a more significant role. This study reiterates the importance of physical exercise in patients with established CVD.

Lead author biography

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

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

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Author contributions

N.E.B. was responsible for designing the work, performing data analyses, interpreting the results, and drafting and revising the manuscript. A.M.M., M.H., J.A.N.D., M.G.v.d.M., Y.M.R., G.J.d.B., and J.M.G. critically interpreted the results and revised the manuscript. F.L.J.V. was responsible for designing the work, interpreting the results, and revising the manuscript and is the manuscript's guarantor. C.K. was responsible for designing the work, interpreting the results, and drafting and revising the manuscript.

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