Lifelong exercise patterns and cardiovascular health

Running head: *Exercise and cardiovascular health*

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ABSTRACT

Objective: To determine the relationship between lifelong exercise dose and the prevalence of cardiovascular morbidity.

Patients and Methods: Between June 2011 and December 2014, 21,266 individuals completed an online questionnaire regarding their lifelong exercise patterns and cardiovascular health status. Cardiovascular disease (CVD) was defined as a diagnosis of myocardial infarction, stroke or heart failure, whereas cardiovascular risk factors (CVRF) were defined as hypertension, hypercholesterolemia, and type 2 diabetes. Lifelong exercise patterns were measured over a median of 32 years for 405 CVD cases, 1,379 CVRF cases, and 10,656 controls. Participants were categorized into non-exercisers and quintiles (Q1 to Q5) of exercise dose (MET-min/week).

Results: CVD/CVRF prevalence was lower for each exercise quintile compared to non-exercisers (CVD: non-exercisers: 9.6% *vs*. Q1: 4.4%, Q2: 2.8%, Q3: 2.4%, Q4: 3.6%, Q5: 3.9%; P<.001; CVRF non-exercisers: 24.6% *vs*. Q1: 13.8%, Q2: 10.2%, Q3: 9.0%, Q4: 9.4%, Q5: 12.0%; P<.001). The lowest exercise dose (Q1) significantly reduced CVD and CVRF prevalence, but the largest reductions were found at a dose of 764-1,091 MET-min/week for CVD ($OR_{adjusted}$: 0.31 [95%CI: 0.20-0.48]) and CVRF ($OR_{adjusted}$: 0.36 [95%CI: 0.28-0.47]). CVD/CVRF prevalence did not further decrease among higher exercise dose groups. Exercise intensity did not influence the relationship between exercise patterns and CVD or CVRF.

Conclusion: Our findings demonstrate a curvilinear relationship between lifelong exercise patterns and cardiovascular morbidity. Low exercise doses can effectively reduce CVD/CVRF prevalence, but engagement of exercise for 764 to 1,091 MET-min/week is associated with the lowest CVD/CVRF prevalence. Higher exercise doses do not yield additional benefits.

KEYWORDS: exercise training, athletes, cardiovascular disease prevention, atherosclerosis, lifestyle

ABBREVIATIONS

CI	Confidence interval
CVD	Cardiovascular disease
MET	Metabolic equivalents of task
OR	Odds ratio
Q	Quintile

INTRODUCTION

Physical inactivity is considered a major modifiable risk factor for all-cause mortality [1, 2], whereas habitual physical exercise reduces the risk of cardiovascular morbidity and mortality [3, 4]. Regular exercise is also associated with increased survival in the general and the athletic population [5-7]. Therefore, the World Health Organization and Centers for Disease Control and Prevention recommend adults to engage in at least 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise per week for optimal cardiovascular and global health [8-10]. These guidelines also state that there is even more benefit from 300 minutes per week of moderate, and 150 minutes of vigorous-intensity exercise.

Such recommendations suggest increasing benefit with increasing exercise dose, but recent studies suggest a potential U-shaped association, indicating that high doses of exercise may abolish the beneficial health effects [11, 12]. Results of the *Copenhagen Heart Study* indicate that vigorous joggers have similar mortality rates as the sedentary non-joggers (hazard ratio: 1.97, 95% CI: 0.48-8.14 and hazard ratio: 0.66, 95% CI: 0.32-1.38, respectively) [11]. The *Million Women Study* indicates that daily strenuous activities increase the risk for stroke and venous thromboembolism compared to strenuous activities performed for 2-3 sessions/week [12]. The notion that exercise might increase the risk for cardiovascular morbidity is striking, but strong evidence is currently lacking.

To confirm or reject the U-shaped association between exercise and cardiovascular morbidity, this study aimed to determine the relationship between lifelong exercise dose and the prevalence of cardiovascular morbidity (myocardial infarction, stroke, and heart failure) in a physically active population. We collected data in 21,266 participants of the Nijmegen Exercise Study (Nijmegen, the Netherlands) and hypothesized that high lifelong exercise doses relate to a decrease in the prevalence of cardiovascular morbidity.

METHODS

Study design and study population

The *Nijmegen Exercise Study* is a population-based study among participants of Dutch sport events and their family members and friends. The study is designed to examine the impact of a physically active lifestyle on health, quality of life, and the development and progression of cardiovascular disease (CVD). Participants of the *International Nijmegen Four Days Marches*, the largest multi-day walking event in the world, and participants of the *Seven Hills Run*, one of the largest road races in the Netherlands, were eligible to participate in the Nijmegen Exercise Study. Furthermore, family members and friends of the participants of both Dutch sport events were also eligible for participation. Between June 2011 and December 2014, inactive and active participants were recruited via newsletters and internet advertisements. Participants completed an online questionnaire about demographic characteristics, anthropometric measures, lifestyle factors, lifelong exercise patterns, cardiovascular health status, and family history of CVD. To assess the impact of lifelong physical exercise patterns on cardiac morbidity, participants with an age ≥35 years were included in the present study. The study adhered to the Declaration of Helsinki. The Local Committee on Research Involving Human Subjects of the region Arnhem and Nijmegen approved the study and all participants gave their written informed consent.

Lifestyle factors

Participants were asked about their smoking status (never, former, or current) and the highest level of education they completed. Level of education was categorized by low (elementary school or basic vocational education), intermediate (secondary vocational education), or high/academic (higher professional education or academic education).

History of cardiovascular diseases

Participants were asked whether (yes/no) and when (age) their physician diagnosed CVD (myocardial infarction, stroke, or heart failure) or presence of cardiovascular risk factors (CVRF) (hypertension, hypercholesterolemia, or diabetes [type 2]). All participants were also queried about their (cardiovascular) medication usage. To validate CVD/CVRF diagnosis, we performed a cross-check with medication usage. Participants with CVD or CVRF, who did not report cardiac medication usage were excluded from the study. Participants were allocated to the control group if they had no cardiac medical history and did not use cardiac medication. When both CVD and CVRF were diagnosed, the participant was allocated to the CVD group. Participants with congenital heart disease, defined as diagnosis of CVD before the age of 35 years, were excluded from further analysis (Figure 1). Participants were also asked whether CVD was present in their immediate biological family (defined as the participant's parents, brothers, and sisters).

Lifelong exercise patterns

The lifelong exercise patterns before the age of CVD/CVRF diagnosis (cases) or age at study participation (controls) were evaluated via an exercise history questionnaire, distinguishing four age-periods: I) 18-29 years, II) 30-49 years, III) 50-64 years, and IV) ≥65 years. Within these categories, participants were asked per period whether (yes/no) they performed exercise with the corresponding (1) exercise time (hours) per week and (2) self-perceived intensity (light / moderate / vigorous). Participants who failed to complete the exercise questionnaire were excluded from the final analysis. Based on Ainsworth's compendium of physical activities [13], we assigned a metabolic equivalent of task (MET) value of 2.5 for light, 4.5 for moderate, and 8.5 for vigorous exercise. MET minutes (MET-min) were calculated by multiplying the exercise time in minutes with the accompanying MET score of the self-perceived intensity [13]. The average weekly amount of lifelong exercise (MET-min/week) was calculated between the age of 18 and the age of CVD/CVRF diagnosis for the cases. Calculations were made for control participants between the age of 18 and age at study participation. Participants were classified into 6 groups: non-exercisers and quintiles of weekly exercise dose (MET-min/week).

Data analysis

The characteristics of non-exercisers and exercisers were summarized with means and standard deviations, or counts and proportions. CVD and CVRF prevalence were determined for each exercise dose quintile. Logistic regression was used to calculate the odds ratios (OR) of CVD with non-exercisers set as the reference category. In the logistic regression analysis, we adjusted for the following potential confounders: age at CVD/CVRF diagnosis (cases) or age of study participation (controls), sex, smoking status, level of education, and CVD family history. To determine the impact of intensity on CVD and CVRF prevalence across exercise dose quintiles, the proportion of light, moderate, and vigorous intensity were calculated per exercise dose quintile. The analysis was performed via a two-way analysis of variance, with factors 1) CVD/CVRF (yes/no) and 2) exercise dose quintiles. All statistical analyses were performed using SPSS 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Statistical significance was assumed at $P<.05$ (two-sided).

RESULTS

Study population

21,266 participants completed the online questionnaire. After the exclusion of participants with cardiovascular risk factors and missing data, 12,440 participants were available for analysis (Figure 1). We calculated the average weekly lifelong exercise dose over a median period of 32 [interquartile range Q_{25}–Q_{75}: 26–39] years for 405 CVD cases, 1,379 CVRF cases, and 10,656 controls. The CVD sample most frequently had a myocardial infarction (51%), followed by heart failure (30%) and stroke (19%) (Table 1). The CVRF sample most frequently had hypertension (72%), followed by hypercholesterolemia (24%) and diabetes (4%) (Table 2). In general, exercisers had a 58% lower risk to develop CVD (adjusted OR: 0.42 (95% CI: 0.29-0.60) and a 56% lower risk to develop CVRF (adjusted OR: 0.44 [95% CI: 0.35-0.55]) compared to the non-exercisers. These associations were consistent regardless of sex, age, smoking status, family history, and level of education (Figure 2).

(Table 1 here).

(Table 2 here).

Exercise dose

Compared to non-exercisers, CVD prevalence was lower in all exercise dose quintiles (non-exercisers: 9.6% *vs*. Q1: 4.4%, Q2: 2.8%, Q3: 2.4%, Q4: 3.6%, Q5: 3.9%; P<.001). After adjustment for age, sex, smoking status, level of education, and CVD family history, the adjusted OR of CVD prevalence to lifelong exercise dose were for Q1) 0.55 [95% CI: 0.36-0.82], Q2) 0.38 [95% CI: 0.25-0.59], Q3) 0.31 [95% CI: 0.20-0.48], Q4) 0.41 [95% CI: 0.27-0.62], and Q5) 0.43 [95% CI: 0.28-0.65] (Figure 3a). Participants who exercised at a dose of 773 to 1,091 MET-min/week (Q3) reported the lowest CVD prevalence, with a risk reduction of 69% compared to the non-exercisers. An exercise dose of 773-1,091 MET-min is equal to a weekly run of 13 to 18 km at a speed of ~8.0 km/h or a weekly walk of 17 to 24 km at a speed of ~5.6 km/h.

CVRF prevalence was also lower in all exercise dose quintiles (non-exercisers: 24.6% *vs*. Q1: 13.8%, Q2: 10.2%, Q3: 9.0%, Q4: 9.4%, Q5: 12.0%; P<.001). After adjustment for age, sex, smoking status, level of education, and CVD family history, the adjusted OR of CVRF prevalence to lifelong exercise dose were for Q1) 0.57 [95% CI: 0.44-0.72], Q2) 0.43 [95% CI: 0.33-0.55], Q3) 0.36 [95% CI: 0.28-0.47], Q4) 0.36 [95% CI: 0.28-0.47], and Q5) 0.47 [95% CI: 0.37-0.60] (Figure 3b). Participants who exercised at a dose of 764 to 1,085 MET-min/week (Q3) reported the lowest CVRF prevalence, with a risk reduction of 64% compared to the non-exercisers.

Exercise intensity

In general, CVD, CVRF, and control participants exercised mostly at a moderate intensity (71%), followed by vigorous intensity (16%) and light intensity (13%). The proportion of light and moderate intensity exercise decreased with higher exercise dose quintiles (P<.001), whereas the proportion of vigorous intensity exercise increased with higher exercise dose quintiles (P<.001). CVD and CVRF participants performed more light intensity exercise compared to controls across quintiles (CVD: $P_{interaction}$=0.028; CVRF $P_{interaction}$=0.001). Proportions of moderate intensity exercise (CVD: P=.48; CVRF: 0.17) and vigorous intensity exercise (CVD: P=.20; CVRF: 0.36) did not differ between CVD/CVRF and controls participants across quintiles (Figure 4).

DISCUSSION

This study presents several major findings. First, exercise below the recommended dose is associated with reduced cardiovascular morbidity. Second, performing exercise at a dose of 764 to 1,091 MET-min per week is associated with the lowest reduction in CVD/CVRF prevalence, approximating 69% for CVD and 64% for CVRF. Third, a higher exercise dose does not yield additional cardiovascular benefits, as we observed that CVD and CVRF prevalence did not further decrease among the highest exercise dose groups. Fourth, these data do not support the presence of the U-shaped association between exercise and CVD prevalence, but reinforce the hypothesis that regular exercise performance is a potent lifestyle intervention to reduce cardiovascular burden.

Several studies reported the favourable health effects of exercise [7, 14-16], as evidenced by reductions in mortality risk in physically active individuals. The present study focused on cardiovascular morbidity only, and demonstrated a reduced CVD and CVRF prevalence across all exercise quintiles. Current exercise guidelines recommended a (minimum) weekly exercise dose of 675 MET-min (five days/week of moderate intensity exercise [~4.5 MET] for 30 minutes/day) [10]. We found in our least active quintile significant cardiovascular benefits of 45% and 43% reduction in CVD and CVRF prevalence, respectively. Q1 participants exercised on average 297 MET-min/week, which is equal to the effort of a weekly 4.8 km run at 8 km/h (~8.3 MET) or 6.4 km walk at 5.6 km/h (~4.3 MET). These findings reinforce previous observations that low doses of exercise can induce significant health effects [14, 15, 17]. The high '*return on investment*' of low exercise doses could encourage inactive and vulnerable populations to start exercise and gain subsequent cardiovascular benefits.

The quest for identification of the optimal exercise dose for cardiovascular health is challenging, since it comprises exercise time, intensity, or a combination of both [18]. The present study, demonstrated the lowest prevalence of CVD and CVRF between 764 to 1,091 MET-min per week which is in agreement with the exercise recommendations of the World Health Organization [10]. This 'optimal' exercise dose is a feasible goal for many individuals and includes 170 to 242 min/week of moderate intensity exercise or 90 to 128 min/week of vigorous intensity exercise. With a reduction of 69% for CVD prevalence and 64% for CVRF prevalence, these exercise doses importantly contribute to primary prevention and hence the reduction of CVD related healthcare expenses.

Interestingly, few studies revealed an upturn in mortality [11, 19] or morbidity [12] risk with higher doses of exercise. The exercise dose of our highest quintile (Q5) is equal to the effort of a weekly ~350-minute run at ~8 km/h (~8.3 MET) or a total running distance of ~47 km/week. Although these extreme exercisers did not report the lowest CVD or CVRF prevalence, a 57% reduction in CVD and 53% reduction in CVRF were found compared to non-exercisers. One might argue that the absence of a further decline in cardiovascular benefits at the higher exercise doses could relate to the amount of vigorous intensity exercise, which these individuals (Q5) experienced. Vigorous endurance exercise is known to induce atherosclerotic plaque rupture [20-22], transient cardiac dysfunction, and cardiac remodelling [22-25]. Indeed, Q5 participants exercised significantly more ($P<.001$) on a vigorous intensity level (47%) compared to all other quintiles (Q1): 3%, Q2): 6%, Q3): 6%, Q4): 16%). However, the proportion of vigorous intensity exercise did not differ between CVD/CVRF and control participants in Q5 (CVD: 50% *vs*. control: 44%; $P=.22$, CVRF: 46% *vs*. control: 44%; $P=.30$). Other studies demonstrated an increased longevity of 2.8 to 6 years among elite athletes with high-intensity exercise compared to reference cohorts [6, 26, 27]. Likewise, Gebel *et al.*, demonstrated that vigorous activity was associated with a strong inverse relationship with mortality in the *45 and Up Study* (n=204,542, aged 45 through 75) [28]. Larger doses of vigorous exercise yielded a larger decline in (cardiovascular) mortality compared to exercise at a moderate intensity level alone. Although, a higher exercise dose does not yield additional health benefits, it is unlikely that the amount of vigorous intensity exercise contributes to this finding.

The present study demonstrates a curvilinear relationship between exercise and cardiovascular health. Hence, our findings contradict recent studies suggesting a potential U-shaped association [11, 12]. There are several explanations for these different study outcomes. The results of the *Copenhagen Heart Study* [11] are difficult to interpret because of the low number of deaths (n=2) in the vigorous exercise group (n=38) [29]. Furthermore, the sedentary (reference) group was allowed to bike or walk for a maximum of 120 min/week [11] suggesting the possibility that they already gained cardiovascular health benefits from these low exercise doses [15]. Hence, the comparison between the 'sedentary' and vigorous exercise group is likely to underestimate the true exercise benefits. Within the '*Million Women Study*' by Armstrong *et al.*, the prevalence of current smokers was surprisingly higher among the daily strenuous exercises compared to those who did strenuous exercise between 1 and 6 times per week (~26% vs. ~15%). The authors acknowledge that even after adjusting for smoking, residual confounding may have occurred, which could explain the increased cardiovascular morbidity in vigorous exercisers.

The main strength of our study is the extensive period of exercise history (32 [interquartile range Q_{25}–Q_{75}: 26–39] years) over which we were able to calculate the exercise dose. Other studies comprised shorter periods or only questioned the exercise characteristics over a single time point [11, 12]. The primary limitation of this study is that the exercise data were entirely dependent on self-report. This limitation is, however, applicable to nearly all epidemiological studies, since virtually no studies have objectively measured lifelong exercise. Similarly, CVD data were obtained by questionnaires, but via cardiovascular medication usage, we confirmed the CVD status of each individual. Despite our effort to correct for all potential confounders, it is possible that residual confounding may have occurred in the present study. Another caveat may be a recall bias regarding the exercise history of the participants. To reduce this potential error to the minimum, participants were blinded to our study hypothesis [30].

Conclusion

The present study demonstrates that a regular low dose of exercise reduces cardiovascular morbidity, with further risk reduction at higher doses. Optimal health benefits were present with 170 to 242 min/week of moderate intensity exercise or 90 to 128 min/week of vigorous-intensity exercise. CVD/CVRF prevalence did not further decrease among higher exercise dose groups. Therefore, our study does not confirm the recently reported U-shaped association between exercise and morbidity in healthy individuals, but suggests a curvilinear relationship between lifelong exercise patterns and cardiovascular health.

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FIGURES LEGENDS

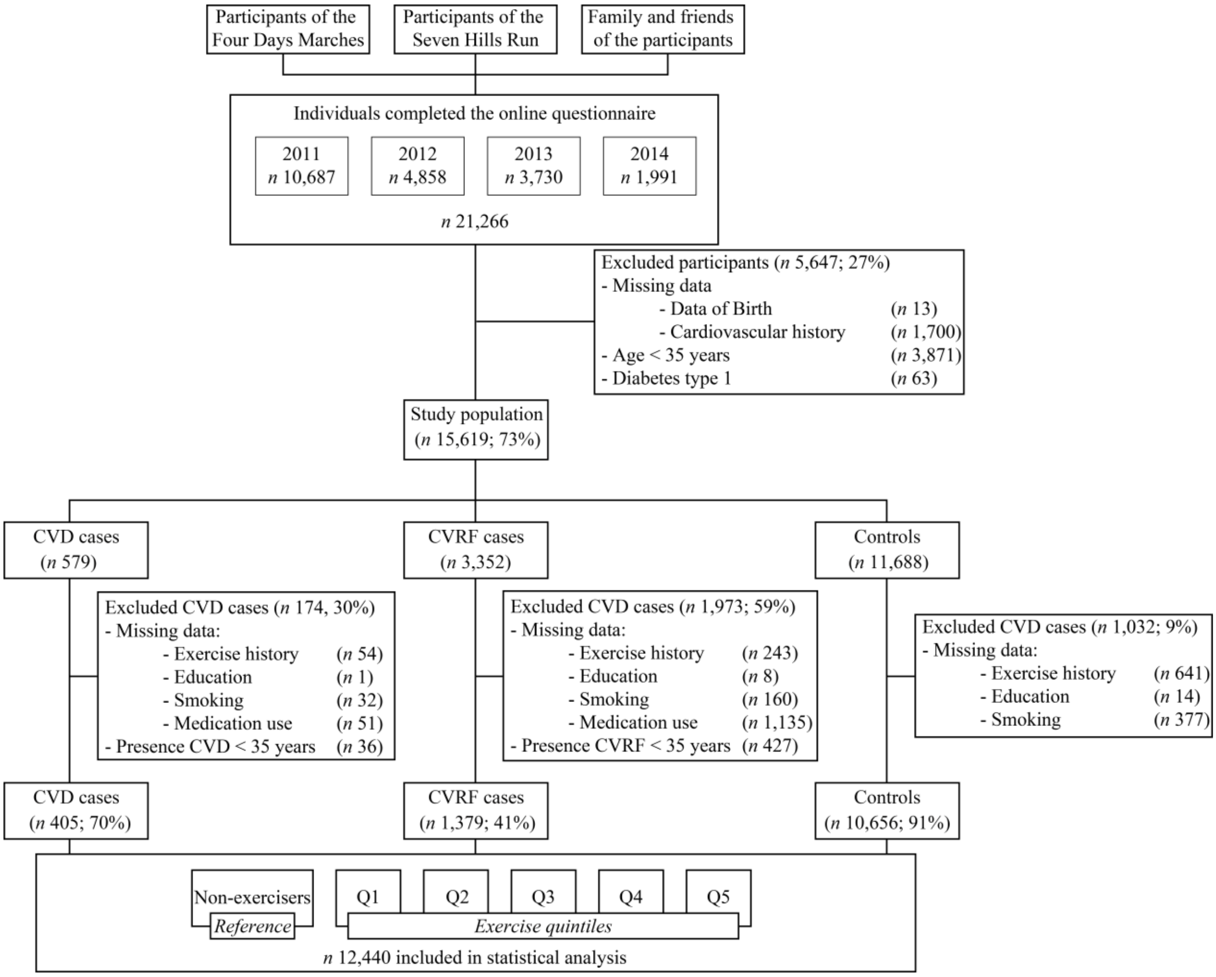

Figure 1. *Flowchart for enrollment of the study population.* 21,266 participants completed the online questionnaire. Initially, 5,647 participants were excluded from the study due to missing data (n=1,713), age below 35 years (n=3,871), diabetes type 1 (n=63). 15,619 participants were divided over three groups (1. CVD cases, 2. CVRF cases, and 3. Controls). We excluded participants with missing data for exercise history (n=938), education (n=23), smoking (n=569), cardiac medication usage (n=1,186), and diagnosis of CVD or CVRF below 35 years of age (n=463). The final study base consisted of 405 CVD cases, 1,379 CVRF cases, and 10,656 controls.

CVD = cardiovascular disease, CVRF = cardiovascular risk factors.

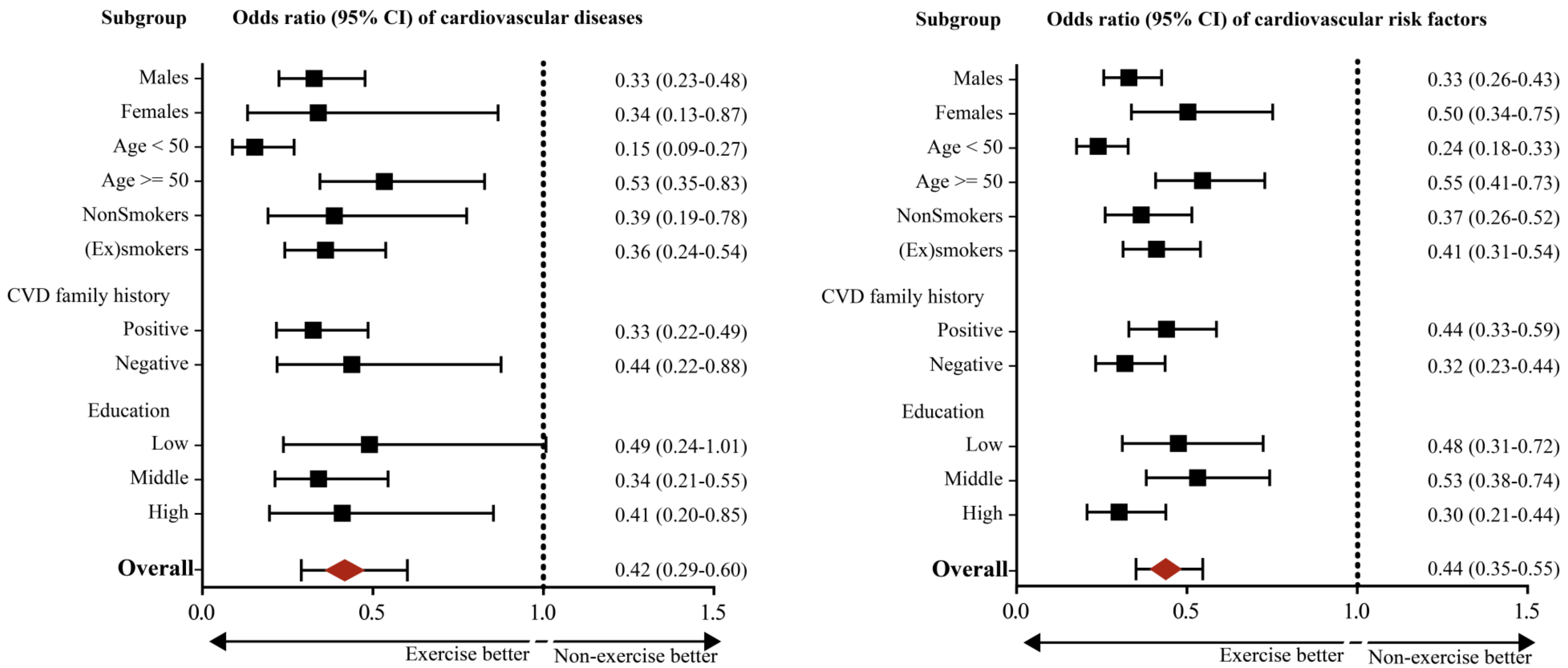

Figure 2. *Odds ratio of cardiovascular disease and cardiovascular risk factors by subgroup*. The reference group analyses includes non-exercisers. Exercisers had a 58% lower risk to develop CVD and a 56% lower risk to develop CVRF compared to the non-exercisers. These associations were consistent regardless of sex, age, smoking status, family history, and level of education. The overall odds ratio (OR) was adjusted for: age, sex, smoking status (never, former, or current smoker), level of education (low, middle, or high education), and CVD family history (positive or negative).

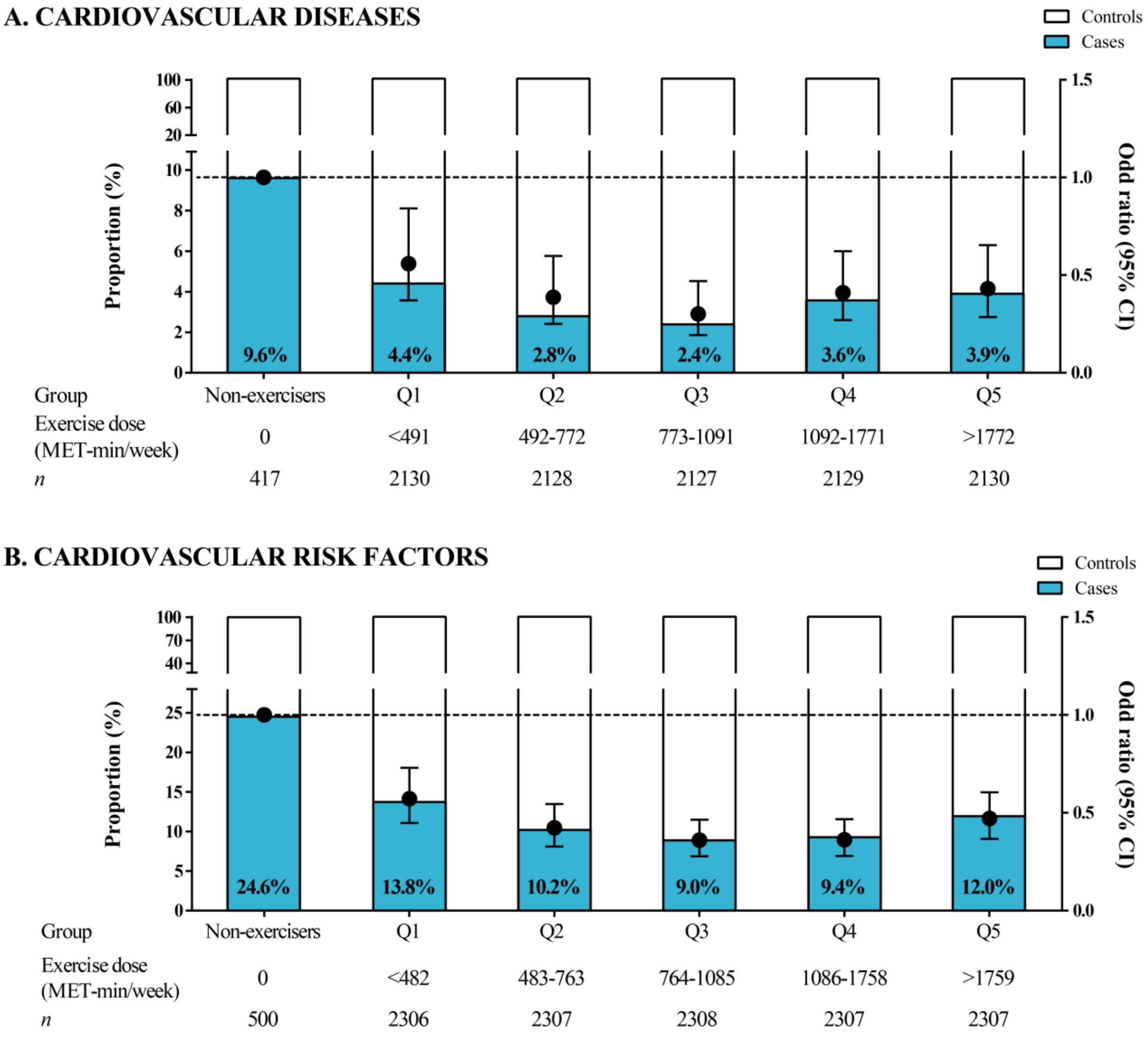

Figure 3. *The association between the prevalence of cardiovascular morbidity and exercise dose per quintile.* The proportion of (A) CVD and (B) CVRF participants per exercise dose (MET-min/week) in quintiles. The left y-axis (bar chart) represents the proportion of participants in the CVD/CVRF and control groups per quintile. The right y-axis (line chart) represents the odds ratio with a 95% confidence interval (CI). The non-exercisers were set as the reference group, where the dotted line represents an odds ratio of one. During the analysis, we adjusted for the following potential confounders: age, sex, smoking status, level of education, and CVD family history.

MET-min/week = Metabolic equivalent of task in minutes per week.

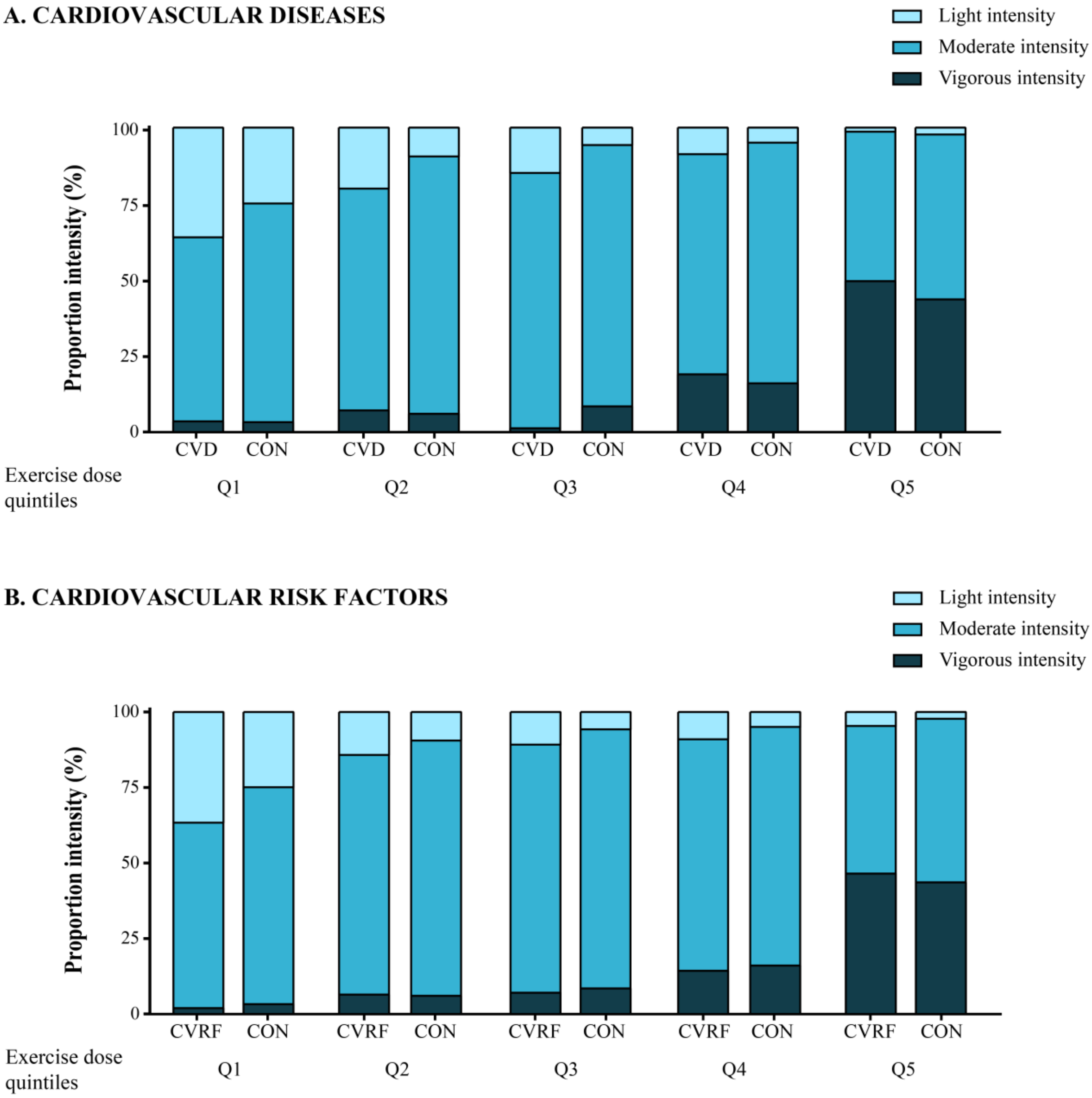

Figure 4. *Proportion of light, moderate, and vigorous intensity per exercise dose quintile.* We categorized the total amount of lifelong exercise dose into light, moderate, and vigorous intensity, based on self-reported perceived intensity of the participant. The bars represent the proportion intensity per exercise dose quintile for control participants versus (A) CVD participants, and (B) CVRF participants. The proportion of light and moderate intensity exercise decreased with higher exercise dose quintiles (P<.001), whereas the proportion of vigorous intensity exercise increased with higher exercise dose quintiles (P<.001). CVD/CVRF cases performed more light intensity exercise across quintiles compared to

controls, whereas moderate and vigorous intensity exercise did not differ between CVD/CVRF cases and controls across quintiles.

CON = controls, CVD = cardiovascular disease cases, CVRF = cardiovascular risk factor cases

Table 1. Characteristics of CVD and control participants within the non-exercisers and exercisers quintiles of lifelong exercise dose (MET-min/week).

Parameter	**Non-exercisers** *n* 417	**Q1** *n* 2,130	**Q2** *n* 2,128	**Q3** *n* 2,127	**Q4** *n* 2,129	**Q5** *n* 2,130
n (%males)	243 (58)	1,047 (49)	1,048 (49)	1,177 (55)	1,348 (63)	1,502 (71)
Age at study participation (years)	53±10	52±10	50±9	49±9	50±9	51±9
Positive family history (n (%))	203 (49)	939 (44)	879 (41)	878 (41)	926 (43)	879 (41)
Lifelong exercise dose (MET-min/week)	0±0	297±122	623±80	924±101	1,388±181	2,909±1,336
Cardiovascular medical history						
Age diagnosis CVD (years)*	53±10	51±10	49±9	49±9	50±9	50±9
n total CVD cases (n (%))	40 (10)	93 (4)	60 (3)	52 (2)	77 (4)	83 (4)
n myocardial infarction (n (%))	27 (6)	43 (2)	31 (1)	22 (1)	41 (2)	43 (2)
n stroke (n (%))	5 (1)	19 (1)	11 (1)	10 (0)	15 (1)	16 (1)
n heart failure (n (%))	8 (2)	31 (1)	18 (1)	20 (1)	21 (1)	24 (1)
Level of education						
Low (n (%))	88 (21)	225 (11)	126 (6)	133 (6)	165 (8)	146 (7)
Intermediate (n (%))	200 (48)	856 (40)	799 (38)	804 (38)	840 (39)	831 (39)
High / academic (n (%))	129 (31)	1,049 (49)	1,203 (57)	1,190 (56)	1,124 (53)	1,153 (54)
Smoking status						
Non-smokers (n (%))	186 (45)	1054 (49)	1137 (53)	1174 (55)	1235 (58)	1307 (61)
Ex-smokers (n (%))	180 (43)	950 (45)	886 (42)	846 (40)	789 (37)	713 (33)
Smokers (n (%))	51 (12)	126 (6)	105 (5)	107 (5)	105 (5)	110 (5)

CVD = cardiovascular disease, MET-min/week = Metabolic equivalent of task in minutes per week.
*CVD cases only

Table 2. Characteristics of CVRF and control participants within the non-exercisers and exercisers quintiles of lifelong exercise dose (MET-min/week).

Parameter	**Non-exercisers** *n* 500	**Q1** *n* 2,306	**Q2** *n* 2,307	**Q3** *n* 2,308	**Q4** *n* 2,307	**Q5** *n* 2,307
n (%males)	301 (60)	1,136 (49)	1,141 (49)	1,282 (56)	1,462 (63)	1,637 (71)
Age at study participation (years)	55±10	52±10	50±9	49±9	51±9	51±9
Positive family history (n (%))	242 (48)	1,047 (45)	995 (43)	969 (42)	1,019 (44)	983 (43)
Lifelong exercise dose (MET-min/week)	0±0	290±120	616±80	919±101	1,386±184	2,918±1,331
Cardiovascular medical history						
Age diagnosis CVRF (years)*	52±9	51±10	49±9	49±9	50±9	50±9
n total CVRF cases (n (%))	123 (25)	318 (14)	236 (10)	208 (9)	218 (9)	276 (12)
n hypertension (n (%))	92 (18)	236 (10)	169 (7)	143 (6)	154 (7)	198 (9)
n hypercholesterolemia (n (%))	24 (5)	69 (3)	57 (2)	56 (2)	56 (2)	68 (3)
n diabetes type 2 (n (%))	7 (1)	13 (1)	10 (0)	9 (0)	8 (0)	10 (0)
Level of education						
Low (n (%))	116 (23)	274 (12)	142 (6)	155 (7)	175 (8)	175 (8)
Intermediate (n (%))	225 (45)	937 (41)	881 (38)	872 (38)	918 (40)	912 (40)
High / academic (n (%))	159 (32)	1,095 (47)	1,284 (56)	1,281 (56)	1,214 (53)	1,220 (53)
Smoking status						
Non-smokers (n (%))	221 (44)	1,111 (48)	1,222 (53)	1,262 (55)	1,323 (57)	1,402 (61)
Ex-smokers (n (%))	224 (45)	1,053 (46)	974 (42)	930 (40)	878 (38)	791 (34)
Smokers (n (%))	55 (11)	142 (6)	111 (5)	116 (5)	106 (5)	114 (5)

CVRF = cardiovascular risk factors, MET-min/week = Metabolic equivalent of task in minutes per week.
*CVRF cases only