Association of Fatal Myocardial Infarction with Physical Activity

- A pooled-analysis of cohort studies

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Abbreviations

BMI	-	Body-mass index
CI	-	Confidence interval
CVD	-	Cardiovascular disease
MET	-	Metabolic equivalent
MI	-	Myocardial infarction
OR	-	Odds ratio
PA	-	Physical activity

SE	-	Standard error

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Abstract

Background

Physical activity (PA) prevents the development and progression of cardiovascular disease (CVD). Few prospective studies exist on the relation between the level of PA and subsequent risk for death during the acute phase of a MI. We assessed the association of fatal MI with PA in a pooled-analysis of prospective cohort studies.

Materials and methods

European cohorts including participants with baseline assessment of PA, conventional cardiovascular risk factors, and available follow-up on MI and death were eligible. Patients with an incident MI were included in the analysis populations. Leisure-time PA was grouped as sedentary, low, moderate, or high based on calculated net weekly energy expenditure. The main outcome measure was fatal MI, instant or at 28 days. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using multivariate random-effects models.

Results

From ten cohorts including a total of 1 495 254 participants, 28 140 patients with an incident MI comprised the study population. A total 4976 (17.7%) were fatal within 28 days – hereof 3101 (62.3%) were classified as instant fatal MI. Compared with sedentary individuals, those with a higher level of PA had lower adjusted odds of instant fatal MI: low PA (OR, 0.79 [95% CI, 0.60-1.04]), moderate PA (0.67 [95% CI, 0.51-0.89]), and high PA (0.55 [95% CI, 0.40-0.76]). Similar results were found for 28-day fatal MI: low PA (0.85 [95% CI, 0.71-1.03]), moderate PA (0.64 [95% CI, 0.51-0.80]), and high PA (0.72 [95% CI, 0.51-1.00]). Findings were consistent across different subgroups including age, sex, body-mass index, diabetes mellitus, and arterial hypertension. Several post-hoc sensitivity analysis substantiated our main results. A low-to-moderate degree of heterogeneity was detected in the instant fatal MI analysis, but not in that of 28-day fatal MI.

Conclusions and implications

Our pooled-analysis demonstrates that a moderate-to-high level of PA is associated with a lower risk of instant and 28-day death in relation to a MI. These findings support the hypothesis that exercise may reduce myocardial damage in the setting of a MI.

Keywords

Pooled-analysis; myocardial infarction; cohort studies; physical activity; mortality.

Introduction

Ischemic heart disease is the leading cause of death worldwide (1,2). Primary prevention of ischemic heart disease thus constitutes a major public health priority. Regular physical activity (PA) has been shown to prevent the development and progression of cardiovascular disease (3–5) and reduce all-cause mortality in a dose-response-like manner in healthy populations (6–9). The cardioprotective effects of PA has earned it a central role in the 2016 European guidelines on cardiovascular disease prevention in clinical practice (10). Although, the biological mechanisms by which PA exerts its cardioprotective effects are poorly understood, the concept of exercise-induced ischemic preconditioning plays a central role in our current understanding (11,12). Preceding repeated ischemia through exercise may stimulate the release of chemical substances and formation of collaterals increasing blood flow, thus reducing ischemic injury in case of a myocardial infarction (MI) (13,14). Experimental animal models have demonstrated reduced infarct sizes associated with exercise (15–18). Accordingly, less myocardial stunning, improved left ventricular function, less ischemia-induced arrhythmias, and improved survival after a cardiac arrest have been documented in patients hospitalized with MI who experience pre-infarction angina; an equivalent of ischemic preconditioning (19). Despite this strong biological basis for cardioprotective effect of PA, prospective studies on the relation between PA and risk for death during the acute phase of a MI are scarce (20,21).

We undertook a pooled-analysis of prospective cohorts to quantitatively assess the association between PA and fatal MI.

Methods

Design, study selection and participants

The study was designed as a collaborative pooled-analysis of cohort studies identified within the Population Science and Public Health nucleus under the European Association of Preventive Cardiology. Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol and a statistical report and analysis plan. European observational cohorts including healthy participants with baseline assessment of PA, conventional cardiovascular risk factors and subsequent follow-up on MI and death (including cause of death) were considered eligible.

Participants who experienced a MI during follow-up were eligible for analysis. Exclusion criteria were: a history of MI prior to baseline assessment or missing data on physical activity or survival status. The final study populations included participants with an incident MI and available follow-up on both in- and out-of-hospital deaths.

All studies fulfilling eligibility criteria, as assessed by a standardized questionnaire, received a joint statistical report and analysis plan specifying variables of interest, data preparation and statistical analyses to be completed locally.

Standardisation of level of physical activity

The exposure variable of interest was level of leisure-time PA at baseline assessment upon entering a cohort. As the studies included in this pooled-analysis measured PA differently (e.g. type of activity, metabolic equivalents [MET]), we standardised and grouped level of PA into four categories based on total weekly energy expenditure (MET-hours per week): sedentary (<7 MET-hrs per week), low (7-16 MET-hrs per week), moderate (16.1-32 MET-hrs per week), and high (>32 MET-hrs per week). This classification was based on applying the conversion rules from the validated International Physical Activity Questionnaire (IPAQ) based on the updated Compendium of Physical Activity (https://sites.google.com/site/compendiumofphysicalactivities/) to the four categories of leisure-time PA used in the Copenhagen City Heart Study questionnaire (21,22). Our cut-off values generally agreed well with those stated in current European guidelines (10). The calculations are shown in the Supplementary Material (Appendix Text).

Main outcome measures and follow-up

The main outcome measure was fatal MI occurring within 28 days of the index event, i.e. case-fatality of MI. Fatal MI was classified as instant if a) date of death coincided with date of MI hospitalization, or b) in the case of out-of-hospital death the cause was registered as MI (ICD-10 code: I21x or I22). Patients who survived the day of index event, but subsequently died within 28 days with MI as the registered cause of death were classified as 28-day fatal MI (23).

Statistical analysis

Cohort level analysis

Each cohort identified all patients with a MI event between baseline assessment and end of follow-up (Appendix Figure 2). The covariates of age, sex, diabetes mellitus, arterial hypertension, family history of CVD, smoking, BMI, total blood cholesterol level, systolic and diastolic blood pressure, alcohol consumption and socioeconomic status were considered potential confounders in the analyses. Aggregated baseline data, numbers of patients and events, and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were provided for pooled-analyses. We used ORs, calculated by logistic regressions with/without adjustments for aforementioned confounders, as our main measure to assess the relation between PA and fatal MI. For each study we converted these values using their natural logarithms. Standard errors (SEs) and variance were calculated from these logarithmic numbers and their corresponding 95% CIs. Our random-effects pooled analyses of the studies were based on these within-study comparisons, thereby avoiding biases caused by methodological differences between studies.

Pooled analysis

Using the group with the lowest weekly net energy expenditure (sedentary) as reference, we estimated the pooled ORs and 95% CIs of fatal MI for the low, moderate, and high categories using both fixed- and random-effects multivariate models. Since the use of a common reference group for all three comparisons within each study is likely to result in correlated effect estimates, we included a variance-covariance matrix in each model as described by Gleser et al. (24) to account for this dependency. We calculated the quantity I^2 using the

method suggested by Viechtbauer et al. (25,26) to describe the degree of heterogeneity with values of 25%, 50%, and 75% considered low, moderate, and high, respectively.

The risk of bias across studies was assessed by plotting the effect by the inverse of its standard error for each study in a funnel plot which was assessed visually and using Egger's regression test. Due to the complexity of our data comparison-adjusted funnel plots were generated using a network meta-analytical approach to our patient and event counts; thus, these results were not adjusted for the listed covariates. Estimates from the network meta-analysis are presented in the Supplementary materials (Appendix Table 3).

To examine the source of heterogeneity, sensitivity analyses were performed according to selected patient characteristics; specifically, pre-specified subgroups of time from baseline assessment to incident MI (<5 years vs. ≥5 years after baseline assessment of PA), age at time of MI (<65 years vs. ≥65 years), sex (male vs. female), body-mass index (<30 kg/m^2 vs. ≥30 kg/m^2), diabetes mellitus (yes vs. no), and arterial hypertension (yes vs. no).

A post-hoc sensitivity analysis was conducted to assess the influence of European region (Scandinavia vs. other European) and identified data uncertainties, i.e. cohorts with no reported data on prior heart failure (yes vs. no), variation in the distribution of patients according to PA group (<40% vs. ≥40% in high PA group) and the observation of a relatively low prevalence of instant fatal MI in some cohorts (<10% vs. ≥10%) which may suggest underreporting of out-of-hospital death.

All analyses were conducted in statistical software R, version 3.4.1 (27). The pooled-analysis was performed using the *metafor* package (26) and the *netmeta* package (28).

Results

A total of 17 European observational cohort studies were invited to participate – three did not respond, three did not fulfil all eligibility criteria, and one study did not have enough data, leaving 10 studies for further analysis (Figure 1). Of the ten cohorts included in the pooled-analysis, three were from Denmark (22,29–31), two from the Netherlands (32,33), one from Norway (34), one from Belgium (35), one from Greece (36), and two from the United Kingdom (37). Table 1 summarises selected characteristics of each cohort study.

From a total of 1 495 254 participants, 28 140 individuals subsequently developed an incident MI and constituted the study population (Appendix Figure 2). Of the 4976 fatal MIs within 28 days, approximately two-thirds (3101 deaths) were classified as instant fatal MI. Table 2 shows the clinical characteristics at baseline assessment of the 28 140 patients who developed an MI. Overall, the distribution of age, sex and cardiovascular risk factors demonstrated significant variation across studies. After weighted pooling of baseline characteristics by level of PA, the sedentary group had the highest prevalence of males, diabetes mellitus and arterial hypertension with a dose-response-like decrease across increasingly higher levels of PA (Appendix Table 1). Notably, the distribution of patients according to PA category displayed significant variation across cohorts, i.e. sedentary [range: 1.0% to 61.6%], low PA [range: 3.1% to 54.5%], moderate PA [range: 6.8% to 36.4%], and high PA [range: 0% to 89.1%].

Figures 2 and 3 summarize unadjusted ORs for instant and 28-day fatal MI for the individual studies along with pooled unadjusted and adjusted ORs. Overall, a higher level of PA was associated with lower risk of instant and 28-day fatal MI, seemingly in a dose-response-like manner. Compared with individuals who were sedentary, the pooled fully adjusted ORs for instant fatal MI were 0.79 (95% CI, 0.60-1.04) for those who pursued low PA, 0.67 (CI, 0.51-0.89) for moderate PA, and 0.55 (CI, 0.40-0.76) for high PA. Estimates for the same comparisons for 28-day fatal MI were 0.85 (CI, 0.71-1.03) for low PA, 0.64 (CI, 0.51-0.80) for moderate PA, and 0.72 (CI, 0.51-1.00) for high PA. Heterogeneity was low-to-moderate in the analyses of instant fatal MI, while no evidence of heterogeneity was detected in the analyses of 28-day fatal MI.

Compared with sedentary individuals, those with higher levels of PA had a lower risk of fatal MI, irrespective of time from baseline assessment to MI, age, sex, a history of diabetes mellitus, or a history of arterial hypertension (Table 3). In individuals with a BMI ≥30 kg/m^2 the reduced risk of 28-day fatal MI observed across other subgroups was seemingly attenuated with higher level of PA, although tests for subgroup interactions did not reach statistical significance (28-day fatal MI [Chi^2 = 3.94; df = 2; *P = 0.14*]). Estimates were consistent across all four subgroups in the post-hoc sensitivity analysis (Appendix Table 5).

Estimates from our unadjusted fixed- and random-effects multivariate models (Appendix Table 2) were consistent with those obtained using a network meta-analysis approach (Appendix Table 3). The funnel plots based on estimates from the network meta-analysis did suggest a slight asymmetry for 28-day fatal MI, i.e. smaller studies demonstrating lower odds in the exposure groups were underrepresented in the analysis (Appendix Figure 1). However, Egger's regression test indicated no significant asymmetry of the funnel plots for instant fatal MI (p=0.715) and 28-day fatal MI (p= 0.495), respectively.

Discussion

This pooled-analysis has quantitively assessed the relation between leisure-time PA and risk of death during a subsequent acute MI. The main finding is that increasing levels of PA are associated with a lower risk of fatal MI, instantly and at 28-days, in a seemingly dose-response-like manner. Compared with individuals who remain sedentary, those participating in moderate- and high-volume PA have a 33% and 45% lower risk of instant fatal MI, while 1-day survivors have a 36% and 28% lower risk of 28-day fatal MI, respectively. Our findings support the hypothesis that PA has cardioprotective capabilities.

The relationship between PA and all-cause mortality has been extensively investigated in the epidemiological literature and a clear biological gradient has been demonstrated; i.e. an increased volume of PA confers with a lower risk for all-cause death in healthy adults (6–9). Similar findings have been reported for cardiovascular disease and death (4,5). To the best of our knowledge only four smaller, observational studies, two of them included in the current pooled-analysis, have addressed the question of how level of PA may modulate the course of a MI in human subjects (20,21,38). Combined these studies suggest that higher level of PA prior to a MI is inversely associated with cardiac biomarker levels, in-hospital death and subsequent cardiovascular events within 1 months of discharge. However, two of these studies did not report out-of-hospital deaths which is likely to result in underestimation of the association (20,38). Our pooled-analysis is consistent with these reported findings, but further extends them by demonstrating that the survival-benefit is immediate,

consistent across clinically relevant subgroups, and preserved at 28 days in patients surviving the first 24 hours of a MI.

Our subgroup analysis showed consistency of the association of fatal MI with PA. The strength of association seemed higher in men and those ≥65 years, but tests for interaction did not reach statistical significance. We also observed an inverse relationship in patients with a body-mass index ≥30 kg/m^2 with an attenuation of the risk estimate across higher levels of PA. Prior studies have shown that factors such as existing cardiorespiratory fitness or the presence of pre-infarction angina may play an important role in these subgroups (38–40); factors unaccounted for in our analysis. The limited number of cohorts and events indicate that the results of our subgroup analysis should be interpreted with caution.

Randomized clinical trials are superior for establishing a causal association, but a scientific question such as ours is very difficult to test under such circumstances. Thus, a pooled-analysis of cohort studies is a potentially powerful approach to assess the relation between fatal MI and PA. The present study includes data from several prospective population-based cohorts, which is a robust design for eliminating selection bias and recall bias.

Our pooled-analysis has several limitations. First, the observational study design warrants special consideration. We were unable to assess changes in level of PA and other cardiovascular risk factors over time in our analysis, which has introduced some inherent measurement error. The relationship between PA and cardiovascular risk factors is complex, multifaceted and time-dependent (41). Although reverse causation could contribute to the findings, stratified analysis by time from baseline assessment of PA to incident MI yielded similar results. Furthermore, potential bias due to other lifestyle measures not measured cannot be excluded. For instance, individuals who participate in moderate-to-high volume exercise may adhere to an overall healthier lifestyle, i.e. a lower intake of salt and saturated fat, lower rates of smoking and less likely to be overweight (42). We did find evidence of such 'healthy adherer effect' in our data (Appendix Table 1). However, adjustments for major CV risk factors had little impact on risk estimates, indicating that residual confounding is not likely to explain our findings. Second, the number of cohorts included in our pooled-analysis was relatively small; a problem encountered in many pooled-analyses. Of the ten included cohorts, only three cohorts accounted for almost 83% of patients and 77% of outcomes, which of course limits overall generalizability of our findings. Third, we could not exclude potential bias due to misclassification of level of PA, cardiovascular risk factors, and fatal MI, as data were collected differently among individual cohort studies. We observed significant heterogeneity between cohorts in all the above. Notably, the distribution of PA was right skewed in the Dutch and UK cohorts, which is likely explained by questionnaires with a high level of detail on PA in these cohorts (Appendix Table 4). Since only a smaller number of cohorts were included, ancillary analysis using i.e. meta-regression to further explore heterogeneity was not meaningful. Finally, prevalence of instant and 28-day fatal MI varied between cohorts, which may be due to selection of participants (43), recruitment period and differences in registration practice of causes of death.

In conclusion our pooled-analysis demonstrates that a moderate-to-high level of physical activity is associated with a lower risk of death in relation to a MI. These findings support the hypothesis that exercise may reduce myocardial damage in the setting of a MI.

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Transparency declaration

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures

… Please see separate Author information sheet.

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Tables

Table 1 Study characteristics of the 10 participating European cohorts

Cohort	Country	Brief description	Recruitment period	Follow-up, years	Total number of participants	Total number of MI during follow-up (fatal outcome at 28 days)
ATTICA	Greece	Participants >18 years and residing in the Attica region within the greater Athens area.	2001-02	10	3042	177 (69)
BELSTRESS	Belgium	Participants aged 35-59 years, who were workers from 25 companies in Belgium.	1994-98	1	13 897	39 (17)
CCHS	Denmark	A random draw from the Danish Civil Registration System of participants aged 20-93 years and residing in Østerbro.	1976-78	34	14 223	1664 (647)
CGPS	Denmark	A random draw from the Danish Civil Registration System of participants aged 20-93 years and residing in Herlev and Østerbro.	2003-14	1-11	104 801	1401 (161)
CONOR	Norway	Consisting of 10 population surveys of adults: Tromsø IV, HUNT II, HUSK, Oslo II, HUBRO, OPPHED, Tromsø V, I-HUBRO, TROFINN, MoRo II.	1994-2003	Ongoing	173 236	9120 (1917)
CRPH	Denmark	Consisting of 5 combined cohorts: MONIKA I, II and III, Inter99, and Health 2006. Random samples of the general population in up to 11 municipalities in the greater Copenhagen area.	1982-2008	Ongoing	17 571	778 (95)
MORGEN-project	The Netherlands	A merged cohort of the MORGEN-EPIC cohort with participants aged 20-59 years residing in Bilthoven.	1993-97	17-21	17 593	337 (53)
Million Women Study	United Kingdom	Recruitment of one in every four UK women born in 1935-50 at 66 NHS breast screening centres.	1996-2001	Ongoing	632 177	10 451 (1509)
Rotterdam study	The Netherlands	Participants aged ≥40 years residing in the Ommord district of Rotterdam.	1990-	Ongoing	14 926	384 (87)
UK Biobank	United Kingdom	Participants 40-69 years of age from the general population.	2006-10	Ongoing	502 536	3789 (421)

BELSTRESS = Belgian Job Stress Study. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CONOR = Cohort of Norway. CRPH = Cohort of the Research for Prevention and Health. MORGEN-project = Monitoring Risicofactoren en Gezondheid in Nederland. UK Biobank = United Kingdom Biobank.

Table 2 Clinical characteristics at baseline assessment for 28 140 patients with subsequent incident MI, by individual cohort

	ATTICA	BELSTRESS	CCHS	CGPS	CONOR	CRPH	MORGEN-project	MWS	Rotterdam study	UK Biobank
No. of patients	177	39	1664	1401	9120	778	337	10 451	384	3789
Age, years	59.1 (13.3)	51.2 (3.7)	64.8 (9.2)	70.1 (11.6)	71.2 (12.6)	51.3 (10.1)	58.1 (8.6)	70.3 (6.6)	70.5 (7.7)	63.0 (6.9)
Male sex, %	70	100	59	63	69	70	69	0	45	73
Diabetes mellitus, %	25	10	5	12	30	7	5	8	17	10
Hypertension, %	44	46	56	27	62	30	40	40	27	34
Family history of CVD, %	32	NA	40	35	53	NA	38	53	21	NA
Active smoking, %	39	72	71	28	36	58	53	58	22	20
BMI, kg/m^2	27.6 (3.7)	28.1 (3.6)	25.9 (4.0)	27.3 (4.2)	27.0 (3.9)	26.6 (4.1)	27.0 (4.2)	26.5 (4.8)	27.1 (3.9)	28.5 (4.6)
Cholesterol, mmol/L	5.5 (1.1)	6.4 (1.1)	6.5 (1.2)	5.9 (1.2)	6.4 (1.2)	6.5 (1.3)	5.8 (1.0)	NA	5.9 (0.9)	5.9 (1.2)
SBP, mmHg	130 (17)	139 (13)	142 (22)	150 (21)	148 (22)	133 (19)	131 (18)	NA	149 (20)	149 (21)
DBP, mmHg	81 (11)	89.3 (13)	85 (12)	86 (12)	83 (12)	NA	82 (11)	NA	78 (11)	85 (11)
Level of physical activity, %										
Sedentary	61.6	28.2	20.8	7.9	42.7	26.7	2.1	2.4	1.0	14.7
Low	11.9	48.7	54.0	50.5	25.6	54.5	4.2	5.8	3.1	16.4
Moderate	9.0	23.1	23.9	36.4	23.3	18.1	9.5	15.2	6.8	20.6
High	17.5	0.0	1.3	5.2	8.4	0.7	84.2	76.6	89.1	48.3
28-day fatal MI, no. (%)	NA	NA	650 (39)	95 (11)	1917 (21)	95 (12)	53 (16)	1509 (14)	87 (23)	421 (11)
Instant	69 (39)	17 (44)	425 (26)	66 (5)	1160 (13)	21 (3)	46 (14)	1220 (12)	27 (7)	21 (1)

BELSTRESS = Belgian Job Stress Study. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CONOR = Cohort of Norway. CRPH = Cohort of the Research for Prevention and Health. CVD = cardiovascular disease. DBP = diastolic blood pressure. MI = myocardial infarction. MORGEN-project = Monitoring Risicofactoren en Gezondheid in Nederland. MWS = the Million Women Study. SBP = systolic blood pressure. UK Biobank = United Kingdom Biobank.
No. are mean (standard deviation) unless otherwise is specified.

Table 3 Pooled odds ratios of fatal myocardial infarction (95% CI) in pooled-analysis, by selected covariates

	Number of cohorts	Number of patients (events)	Level of physical activity				
			Sedentary	Low	Moderate	High	I^2, %
Instant fatal MI							
Time from baseline to MI							
< 5 years	5	6110 (815)	1	0.72 (0.54-0.96)	0.70 (0.52-0.94)	0.60 (0.43-0.85)	19.2
≥ 5 years	6	16 910 (2188)	1	0.68 (0.47-0.99)	0.60 (0.41-0.87)	0.52 (0.36-0.76)	73.1
Age at baseline							
< 65 years	6	6336 (460)	1	0.86 (0.63-1.16)	0.82 (0.61-1.01)	0.71 (0.51-1.00)	<0.1
≥ 65 years	5	17 169 (2527)	1	0.63 (0.45-0.89)	0.57 (0.40-0.81)	0.50 (0.35-0.71)	75.2
Sex							
Males	6	9060 (1180)	1	0.51 (0.19-1.32)	0.47 (0.18-1.24)	0.29 (0.11-0.76)	94.4
Females	6	14 690 (1823)	1	0.75 (0.57-0.98)	0.65 (0.49-0.86)	0.59 (0.45-0.78)	40.0
Body-mass index							
< 30 kg/m^2	7	18 666 (2270)	1	0.71 (0.56-0.91)	0.62 (0.49-0.80)	0.55 (0.43-0.72)	40.3
≥ 30 kg/m^2	5	4224 (596)	1	0.79 (0.53-1.17)	0.74 (0.49-1.10)	0.70 (0.46-1.06)	36.5
Diabetes mellitus							
Yes	5	3824 (591)	1	0.73 (0.51-1.06)	0.71 (0.48-1.05)	0.58 (0.38-0.88)	17.1
No	5	18 830 (2357)	1	0.65 (0.41-1.02)	0.57 (0.35-0.92)	0.62 (0.36-1.08)	27.6
Arterial hypertension							
Yes	6	11 462 (1735)	1	0.81 (0.66-1.00)	0.70 (0.56-0.87)	0.65 (0.51-0.83)	21.2
No	5	11 552 (1232)	1	0.65 (0.49-0.87)	0.67 (0.49-0.90)	0.56 (0.41-0.75)	43.5
28-day fatal MI							
Time from baseline to MI							
< 5 years	6	6476 (394)	1	0.78 (0.58-1.05)	0.69 (0.49-0.96)	0.62 (0.41-0.94)	<0.1
≥ 5 years	6	14 858 (1417)	1	0.79 (0.67-0.93)	0.65 (0.54-0.78)	0.70 (0.58-0.86)	<0.1
Age at baseline							
< 65 years	5	6771 (281)	1	0.87 (0.59-1.28)	0.81 (0.53-1.23)	0.78 (0.50-1.23)	17.0
≥ 65 years	5	14 107 (1515)	1	0.76 (0.65-0.89)	0.60 (0.50-0.71)	0.63 (0.52-0.76)	<0.1
Sex							
Males	5	9336 (1014)	1	0.72 (0.60-0.87)	0.66 (0.54-0.80)	0.71 (0.57-0.89)	<0.1
Females	6	12 020 (797)	1	0.86 (0.69-1.07)	0.54 (0.41-0.72)	0.59 (0.44-0.80)	<0.1
Body-mass index							
< 30 kg/m^2	6	16 504 (1402)	1	0.79 (0.68-0.93)	0.59 (0.49-0.70)	0.59 (0.48-0.73)	<0.1
≥ 30 kg/m^2	6	4242 (377)	1	0.74 (0.51-1.08)	0.85 (0.58-1.26)	1.00 (0.68-1.47)	9.2
Diabetes mellitus							
Yes	3	2104 (293)	1	0.65 (0.49-0.86)	0.54 (0.38-0.79)	0.60 (0.31-1.16)	<0.1
No	3	6671 (747)	1	0.81 (0.53-1.25)	0.62 (0.40-0.97)	0.45 (0.27-0.77)	68.9
Arterial hypertension							
Yes	5	9077 (1034)	1	0.85 (0.70-1.02)	0.54 (0.44-0.67)	0.56 (0.45-0.71)	3.7
No	5	11 063 (707)	1	0.72 (0.57-0.90)	0.56 (0.44-0.73)	0.70 (0.54-0.91)	<0.1

CI = confidence interval. All odds ratios were adjusted for age and sex prior to pooled-analysis. No test for interaction between level of PA and subgroup reached a two-sided statistical significance level of 0.10.

Figures

Figure 1 Flow diagram displaying the cohort selection process

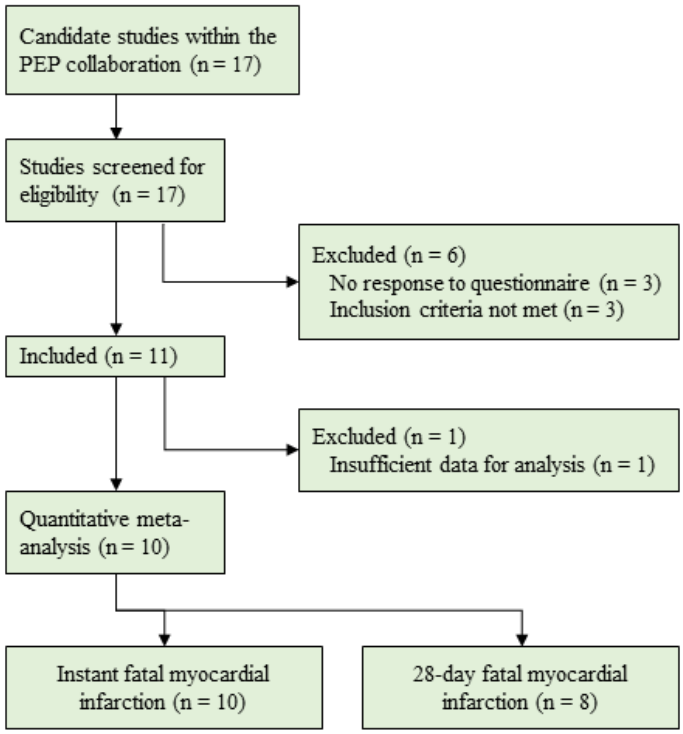


Figure 2 Forest plot for instant fatal myocardial infarction, by exposure contrast using sedentary as reference.

CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CONOR = Cohort of Norway. CRPH = Cohort of the Research for Prevention and Health. MORGEN-project = Monitoring Risicofactoren en Gezondheid in Nederland. PA = physical activity. RE = random-effects. UK Biobank = United Kingdom Biobank.

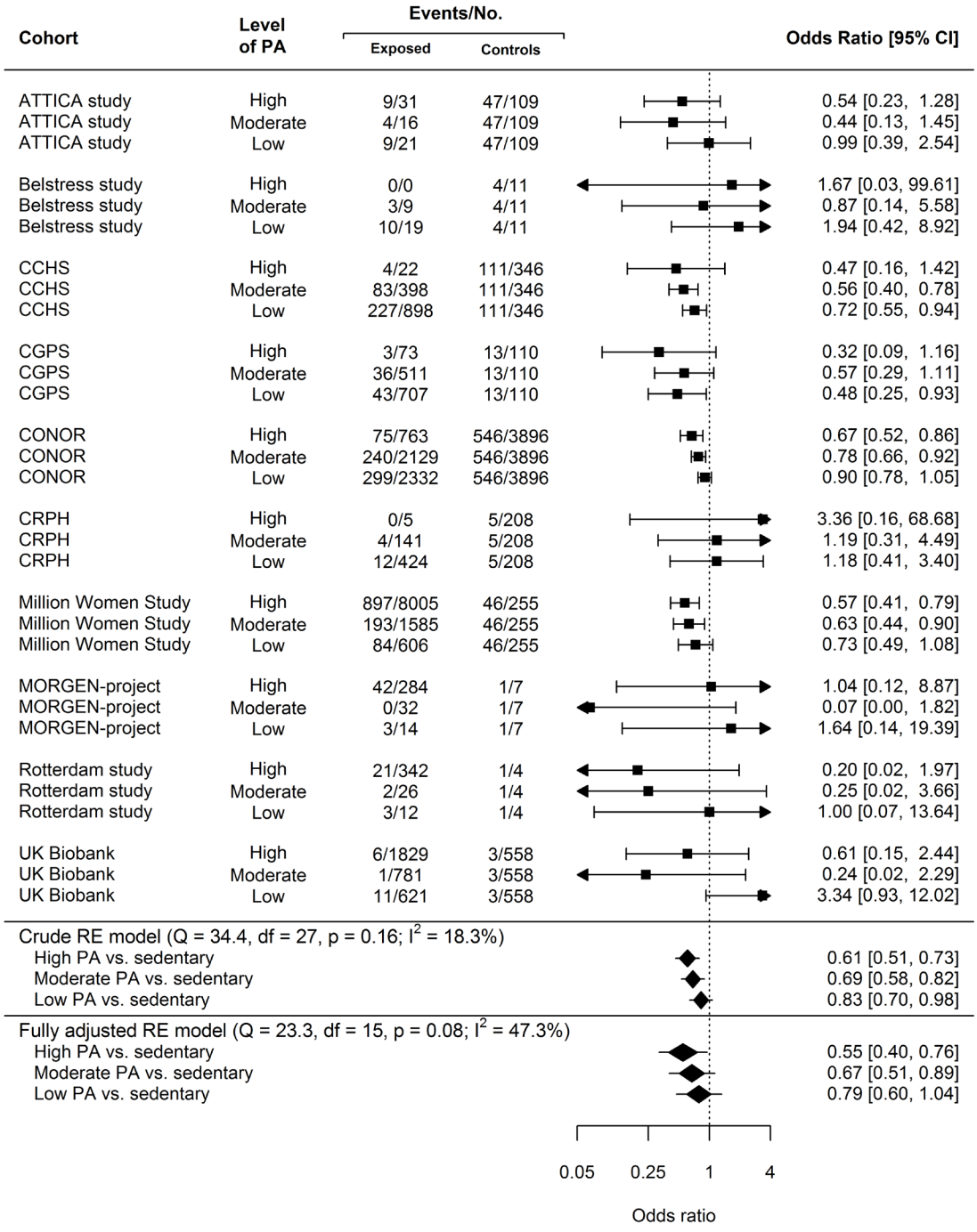
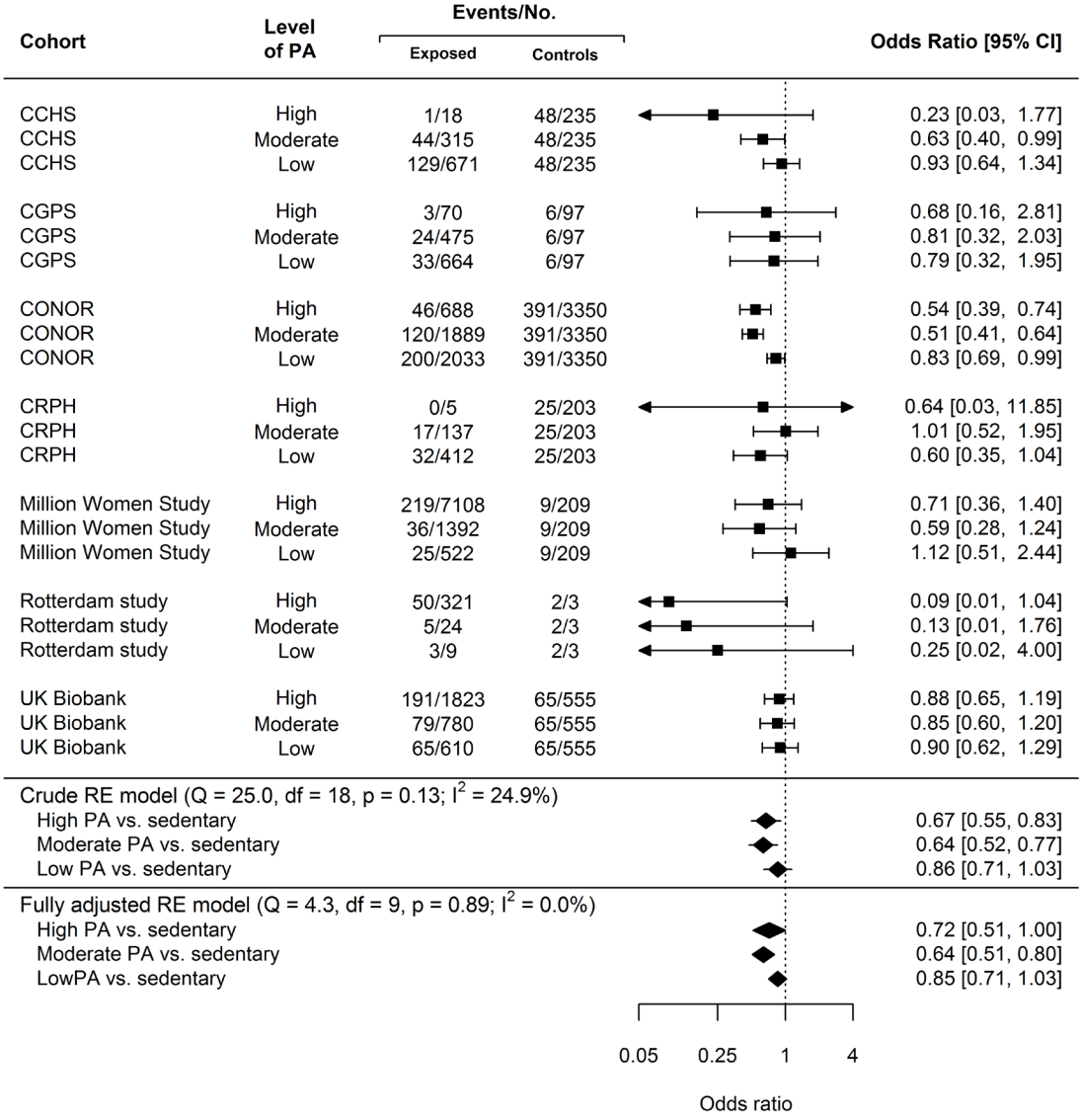


Figure 3 Forest plot for 28-day fatal myocardial infarction, by exposure contrast using sedentary as reference

CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CONOR = Cohort of Norway. CRPH = Cohort of the Research for Prevention and Health. PA = physical activity. RE = random-effects. UK Biobank = United Kingdom Biobank.



Association of Fatal Myocardial Infarction with Physical Activity

- A pooled-analysis of cohort studies

Supplementary Material

Appendix tables

Appendix table 1: Pooled baseline characteristics for patients with MI, by level of PA

Appendix Table 1 Pooled baseline characteristics for patients with myocardial infarction, by level of physical activity

	Level of physical activity			
	Sedentary	**Low**	**Moderate**	**High**
No. Patients	5504	5654	5628	11 354
Demographics:				
Age, years	69.1 (11.6)	68.4 (10.5)	67.7 (10.1)	68.9 (7.5)
Males, %	59.3	59.4	54.0	22.0
Risk factors:				
Diabetes mellitus, %	27.6	18.2	13.6	8.5
Arterial hypertension, %	57.7	51.0	47.2	39.2
Family history of CVD, %	50.2	49.1	48.9	51.3
Active smoking, %	43.0	41.7	39.8	48.5
Biometrics:				
Body-mass index [kg/m^2]	27.6 (4.5)	26.9 (4.1)	26.9 (4.2)	26.7 (4.5)
Total cholesterol [mmol/L]	6.4 (1.3)	6.4 (1.3)	6.2 (1.1)	6.0 (1.2)
Systolic blood pressure [mmHg]	147.3 (22.7)	145.8 (21.2)	144.9 (20.6)	145.4 (19.6)
Diastolic blood pressure [mmHg]	83.8 (12.3)	84.6 (12.0)	84.1 (11.5)	83.6 (10.8)

CVD = Cardiovascular disease. Numbers are mean (standard deviation) unless otherwise is specified. Each characteristic was weighted by [cohort sample size/total sample size].

Appendix table 2: Pooled ORs, 95% CIs, and I^2 statistics for fixed- and random-effects multivariate models

Appendix Table 2 Pooled odds ratios, 95% confidence intervals, and I^2 statistics for fixed- and random-effects multivariate models

			Level of physical activity								
			Fixed-effects models				Random-effects models				
	Number of cohorts	Number of patients (events)	Sedentary	Low	Moderate	High	Sedentary	Low	Moderate	High	I^2, %
Instant fatal MI											
Unadjusted	10	28 140 (3101)	1	0.86 (0.76-0.97)	0.72 (0.63-0.81)	0.63 (0.55-0.72)	1	0.83 (0.70-0.98)	0.69 (0.58-0.82)	0.61 (0.51-0.73)	18.3
Adjustment											
Age and sex	9	27 798 (3055)	1	0.82 (0.73-0.93)	0.73 (0.64-0.82)	0.62 (0.53-0.71)	1	0.74 (0.59-0.93)	0.65 (0.52-0.82)	0.56 (0.44-0.70)	44.5
Age, sex, and CVD risk factors	6	26 602 (2990)	1	0.85 (0.75-0.97)	0.76 (0.66-0.87)	0.65 (0.54-0.79)	1	0.76 (0.59-0.97)	0.67 (0.52-0.86)	0.58 (0.44-0.77)	49.0
Age, sex, CVD risk factors, alcohol consumption, smoking, and socioeconomic status	6	26 602 (2990)	1	0.90 (0.78-1.03)	0.77 (0.66-0.90)	0.63 (0.50-0.80)	1	0.79 (0.60-1.04)	0.67 (0.51-0.89)	0.55 (0.40-0.76)	47.3
28-day fatal MI											
Unadjusted	7	24 618 (1868)	1	0.82 (0.72-0.94)	0.61 (0.53-0.71)	0.66 (0.56-0.78)	1	0.86 (0.71-1.03)	0.64 (0.52-0.77)	0.67 (0.55-0.83)	24.9
Adjustment											
Age and sex	6	24 256 (1808)	1	0.78 (0.68-0.90)	0.63 (0.54-0.73)	0.66 (0.56-0.79)	1	0.78 (0.68-0.90)	0.63 (0.54-0.73)	0.66 (0.56-0.79)	<0.1
Age, sex, and CVD risk factors	6	24 256 (1808)	1	0.78 (0.67-0.90)	0.64 (0.54-0.75)	0.69 (0.56-0.84)	1	0.78 (0.67-0.90)	0.64 (0.54-0.75)	0.69 (0.56-0.84)	<0.1
Age, sex, CVD risk factors, alcohol consumption, smoking, and socioeconomic status	4	19 736 (1334)	1	0.85 (0.71-1.03)	0.64 (0.51-0.80)	0.72 (0.51-1.00)	1	0.85 (0.71-1.03)	0.64 (0.51-0.80)	0.72 (0.51-1.00)	<0.1

CI = confidence interval. CVD = cardiovascular disease. CVD risk factors include diabetes mellitus, arterial hypertension, family history of CVD, total cholesterol levels, and body-mass index.

Appendix table 3: Pooled ORs, 95% Cis, and I^2 statistics for fixed- and random-effects network meta-analysis

Appendix Table 3	**Pooled odds ratios, 95% confidence intervals, and I^2 statistics for fixed- and random-effects network meta-analysis**									
			Level of physical activity				**Heterogeneity**			
	Number of cohorts	**Number of patients (events)**	**Sedentary**	**Low**	**Moderate**	**High**	**Q**	**d.f.**	**p-value**	**I^2, %**
Instant fatal MI										
FE model	10	28 140 (3101)	1	0.86 (0.76-0.97)	0.72 (0.63-0.81)	0.63 (0.55-0.72)	-	-	-	-
RE model	10	28 140 (3101)	1	0.84 (0.76-1.01)	0.68 (0.56-0.83)	0.59 (0.47-0.72)	32.6	26	0.17	20.2
28-day fatal MI										
FE model	7	24 618 (1868)	1	0.82 (0.72-0.94)	0.61 (0.53-0.71)	0.66 (0.56-0.78)	-	-	-	-
RE model	7	24 618 (1868)	1	0.84 (0.68-1.03)	0.65 (0.53-0.81)	0.65 (0.52-0.83)	25.1	18	0.12	28.2
FE = fixed-effects. RE = random-effects.										

Appendix table 4: Assessment of PA, by individual cohort

Appendix Table 4 Assessment of physical activity, by individual cohort							
			Assessment of physical activity				
Cohort	Country	Recruitment period	Method	No. of items	Time frame		
					1 week	4 weeks	1 year
ATTICA	Greece	2001-02	SRQ	7	x		
Belstress	Belgium	1994-98	SRQ	1	x		
CCHS	Denmark	1976-78	SRQ	1			x
CGPS	Denmark	2003-14	SRQ	1			x
CONOR	Norway	1994-2003	SRQ	2			x
CRPH	Denmark	1982-2008	SRQ	5	x		
MWS	United Kingdom	1996-2001	SRQ	2	x		
MORGEN-Project	The Netherlands	1993-97	SRQ	4			x
Rotterdam study	The Netherlands	1990-	SRQ	28	x		
UK Biobank	United Kingdom	2006-10	SRQ	11		x	
SRQ = self-reported questionnaire							

Appendix table 5: Post-hoc analysis of pooled ORs, 95% CIs, and I^2 statistics, by selected cohort characteristics

Appendix Table 5 Post-hoc analysis of pooled odds ratios (95% CIs) for instant fatal myocardial infarction, by selected cohort characteristics

	Number of cohorts	Number of patients (events)	Level of physical activity				
			Sedentary	Low	Moderate	High	I^2, %
Region							
Scandinavia	4	12 958 (1701)	1	0.71 (0.51-0.98)	0.66 (0.47-0.92)	0.56 (0.38-0.84)	64.4
Other European	5	14 840 (1354)	1	0.81 (0.58-1.15)	0.60 (0.43-0.82)	0.54 (0.40-0.72)	<0.1
Information on prior heart failure							
Yes	6	23 197 (2996)	1	0.68 (0.53-0.88)	0.61 (0.47-0.79)	0.53 (0.41-0.69)	60.1
No	3	4601 (59)	1	1.64 (0.77-3.46)	0.88 (0.32-2.45)	0.39 (0.13-1.23)	<0.1
Proportion of cohort in high PA group							
<40%	6	13 174 (1787)	1	0.71 (0.53-0.94)	0.65 (0.48-0.88)	0.55 (0.38-0.79)	50.4
≥40%	3	14 624 (1268)	1	0.83 (0.57-1.20)	0.61 (0.44-0.86)	0.55 (0.40-0.75)	<0.1
Prevalence of instant fatal MI							
<10%	4	6347 (164)	1	0.83 (0.37-1.89)	0.73 (0.31-1.72)	0.29 (0.12-0.74)	55.3
≥10%	5	21 451 (2891)	1	0.75 (0.60-0.95)	0.67 (0.53-0.84)	0.59 (0.46-0.75)	52.7

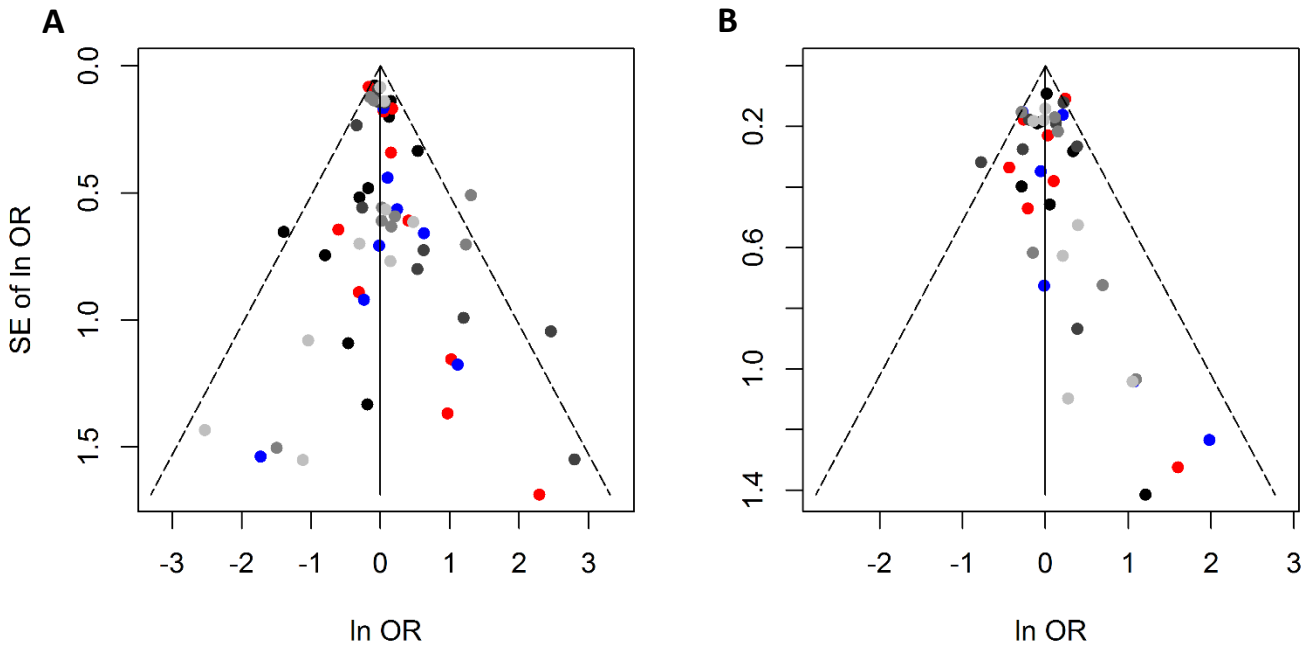
CI = confidence interval. MI = myocardial infarction. PA = physical activity All estimates have been adjusted for age and sex.

Appendix figures

Appendix figure 1: Comparison-adjusted funnel plots

Appendix figure 1 Comparison-adjusted funnel plots displaying the natural logarithms of odds ratios against their SEs for (A) instant and (B) 28-day fatal MI, respectively.

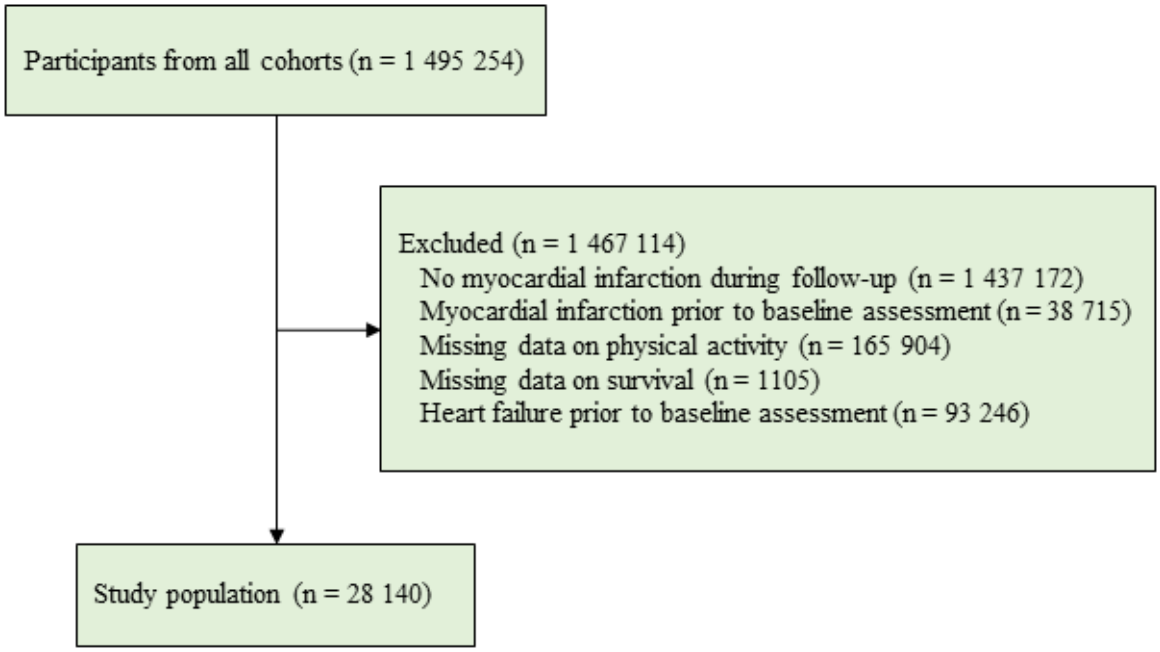
Dots represent study-specific comparisons: black = low vs. sedentary ; red = moderate vs. sedentary ; blue = high vs. sedentary ; dark grey = moderate vs. low ; grey = high vs. low ; light grey = high vs. moderate.



Appendix figure 2: Flow diagram summarizing the derivation of the study population

Appendix figure 2 Flow diagram summarizing the derivation of the study population.

Please note that a participant may meet more than one exclusion criteria.



Appendix text

Standardisation of level of physical activity

Current guidelines recommend that healthy adults of all ages engage in at least 150 minutes of moderate intensity or 75 minutes a week of vigorous intensity PA or an equivalent combination thereof; for additional benefit these durations may be doubled (10). This confers with approximate minimum values of weekly net energy expenditure of 7.5 to 14.75 MET-hrs, or 15 to 29.5 MET-hrs, respectively.

Intensity of PA	IPAQ-based conversion rule
Walking (MET-min/week)	3.3 x minutes of walking x walking days
Moderate (MET-min/week)	4.0 x minutes of moderate intensity activity x moderate intensity activity days
Vigorous (MET-min/week)	8.0 x minutes of vigorous intensity activity x vigorous intensity activity days
Cumulative PA (MET-hrs per week)	(Walking MET-min/week + Moderate MET-min/week + Vigorous MET-min/week) / 60 min/hrs

IPAQ = International Physical Activity Questionnaire. MET = metabolic equivalents. PA = physical activity

Applying the above conversion algorithm to the categorization of leisure-time PA used in the Copenhagen City Heart Study (21,22):

CCHS PA category	IPAQ-based calculation
Inactive or light physical activity <2 hours per week	(3.3 x 120 minutes x 1 day) / 60 min/hrs ≈ 7 MET-hrs/week
Light physical activity 2-4 hours per week	(4.0 x (120 to 240 minutes x 1 day) / 60 min/hrs ≈ 7 to 16 MET-hrs/week
Light activity >4 hours per week or strenuous activity 2-4 hours per week	(4.0 x (>240 minutes x 1 day) / 60 min/hrs ≈ > 16 MET-hrs/week (8.0 x (120 to 240 minutes x 1 day) / 60 min/hrs ≈ 16 to 32 MET-hrs/week
Strenuous activity >4 hours per week or hard training	(8.0 x (>240 minutes x 1 day) / 60 min/hrs ≈ > 32 MET-hrs/week

IPAQ = International Physical Activity Questionnaire. MET = metabolic equivalents. PA = physical activity

These cut-off values are in excellent agreement with those stated in the 2016 European Guidelines of Cardiovascular Prevention in Clinical Practice (10) as shown above.