# Association of Fatal Myocardial Infarction with Past Level of 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 |

# Abstract

## Aims

To assess the association between past level of physical activity (PA) and risk for death during the acute phase of a myocardial infarction (MI) in a pooled analysis of cohort studies.

## Materials

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. Leisure-time PA was grouped as sedentary (<7 MET-hrs), low (7-16 MET-hrs), moderate (16.1-32 MET-hrs), or high (>32 MET-hrs) based on calculated net weekly energy expenditure. The main outcome measures were instant and 28-day case-fatality of MI. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using multivariate random-effects models. Adjustments for age, sex, cardiovascular risk factors, alcohol consumption, and socioeconomic status were made.

## 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 of 4976 (17.7%) died within 28 days – of these 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 [0.51-0.89]), and high PA (0.55 [0.40-0.76]). Similar results were found for 28-day fatal MI: low PA (0.85 [0.71-1.03]), moderate PA (0.64 [0.51-0.80]), and high PA (0.72 [0.51-1.00]). A low-to-moderate degree of heterogeneity was detected in the analysis of instant fatal MI ($I^2$ = 47.3%), but not in that of 28-day fatal MI ($I^2$ = 0.0%).

## Conclusion

A moderate-to-high level of PA was associated with a lower risk of instant and 28-day death in relation to a MI.

## Keywords

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

# Introduction

Ischemic heart disease (IHD) is the leading cause of death worldwide (1,2). Primary prevention of IHD 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 have 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, less ischemia-induced arrhythmias, improved left ventricular function, 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 a cardioprotective effect of PA, prospective studies on the relation between PA and risk for death during the acute phase of a MI are scarce (20–22).

We undertook a pooled analysis of prospective cohorts to quantitatively assess the association between PA and subsequent risk for death during the acute phase of a 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 physical activity level

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 (21,23). 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 (24).

## Statistical analysis

### Cohort level analysis

Each cohort identified all patients suffering a MI event after baseline assessment during 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 level 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. (25) to account for this dependency. We calculated the quantity $I^2$ using the method suggested by Viechtbauer et al. (26,27) 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), first year of recruitment (before 1990 vs. between 1990 and 2000 vs. after 2000), 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 (28). The pooled analysis was performed using the *metafor* package (27) and the *netmeta* package (29).

# 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 (23,30–32), two from the Netherlands (33,34), one from Norway (35), one from Belgium (36), one from Greece (37), and two from the United Kingdom (38). Appendix 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 during follow-up 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~~1 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 graded decrease across increasingly higher levels of PA (Appendix Table 2). 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 2). In individuals with a BMI ≥30 kg/m$^2$ the lower 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 five subgroups in the post-hoc sensitivity analysis (Appendix Table 7).

Estimates from our unadjusted fixed- and random-effects multivariate models (Appendix Table 3) were consistent with those obtained using a network meta-analysis approach (Appendix Table 4). 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

## Key findings

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

## Interpretation

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 PA level confers 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 PA levels may modulate the course of a MI in human subjects (20,21,39). Combined these studies suggested that higher PA levels prior to a MI were 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 (20,39). 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 and heterogeneity was found to be high in these subgroups. We also observed an inverse relationship in patients with a BMI ≥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 (39–41); 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 powerful approach to assess the relation between fatal MI and PA. The present study included data from several prospective population-based cohorts, which is a robust design for eliminating selection and recall biases.

Our pooled analysis provides strong support for the recommendations on weekly PA in healthy adults stated in the 2016 European Guidelines on cardiovascular disease prevention in clinical practice (10); especially as we used cut-off values for PA comparable to those used in the guidelines. We believe that our findings may be helpful to all health providers in their consultancy of healthy adults.

## Study limitations

Our pooled analysis has several limitations. First, the observational study design warrants special consideration. We were unable to assess changes in PA levels 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 (42). 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 could not 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 (43). 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 was unlikely 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, just three studies, i.e. the Copenhagen City Heart Study, the Cohort of Norway, and the Million Women Study, accounted for almost 83% of patients and 77% of outcomes (Appendix Table 6). This, and the fact that nine out of ten cohorts originated from Northern Europe, limits overall generalizability of our findings. The inclusion of several smaller cohorts may have resulted in the moderate-to-high level of heterogeneity observed in our subgroup analyses. Third, we could not exclude potential bias due to misclassification of PA levels, 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 the very detailed PA questionnaires used in these cohorts (Appendix Table 5). Since only a smaller number of cohorts were included, ancillary analysis i.e. using meta-regression to further explore heterogeneity was not meaningful. Fourth, prevalence of instant and 28-day fatal MI varied between cohorts, which may be due to selection of participants (44), recruitment period and differences in registration practice of causes of death. Specifically, the out-of-hospital registration of cause-of-death may have been associated with some inaccuracies. We addressed this issue by including only MI in our main outcome measure as opposed to a broader definition of chronic CAD. This restrictive approach may increase specificity while decreasing sensitivity (45). Finally, we find it highly unlikely that any inaccuracies in the cause-of-death registration was associated with PA level.

In conclusion, 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 acute phase of a MI.

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## Conflict of interests

None declared.

## Authors' contributions

KWH, NP, DP, VV, ML. PMV and EP participated in study design. KWH and EP obtained funding. KWH performed data analysis and wrote the report. All authors interpreted the results, revised the report and approved the final version.

## 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. Aggregated data from each study cohort may be made available upon request.

## Ethics approval

The study protocols of each participating cohort were approved by local ethics committees. This pooled analysis of aggregated data did not require further ethical approval.

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# Tables

**Table 1 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 2 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.

Figure 1 Flow diagram displaying the cohort selection process

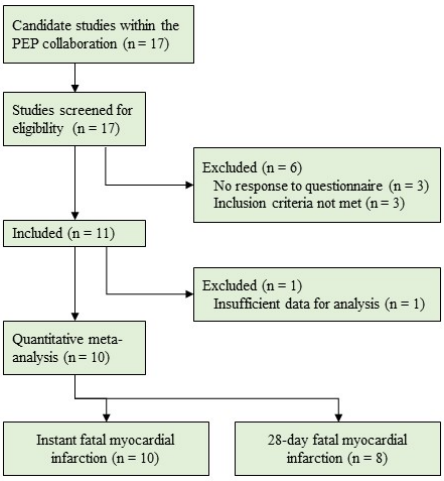
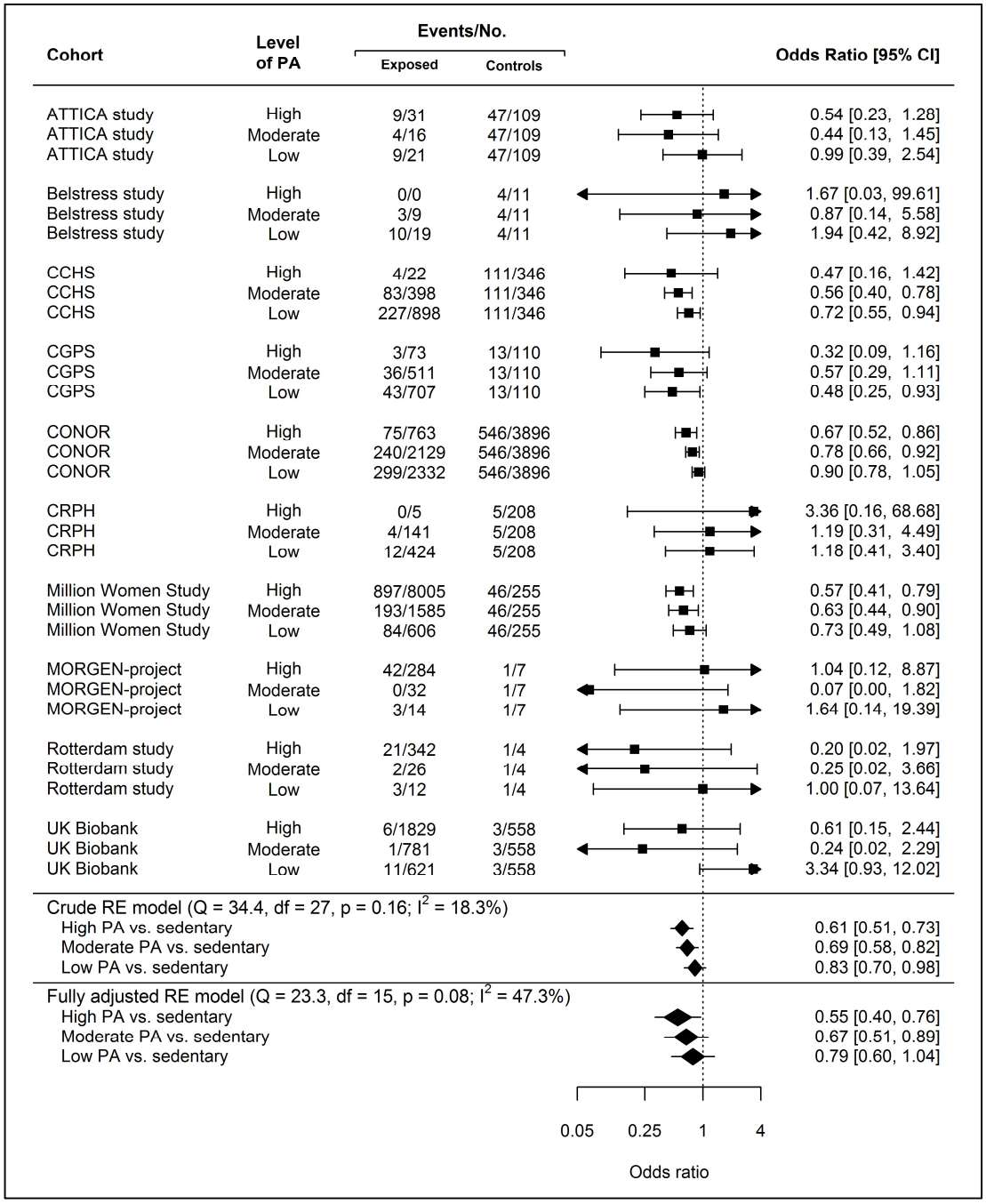
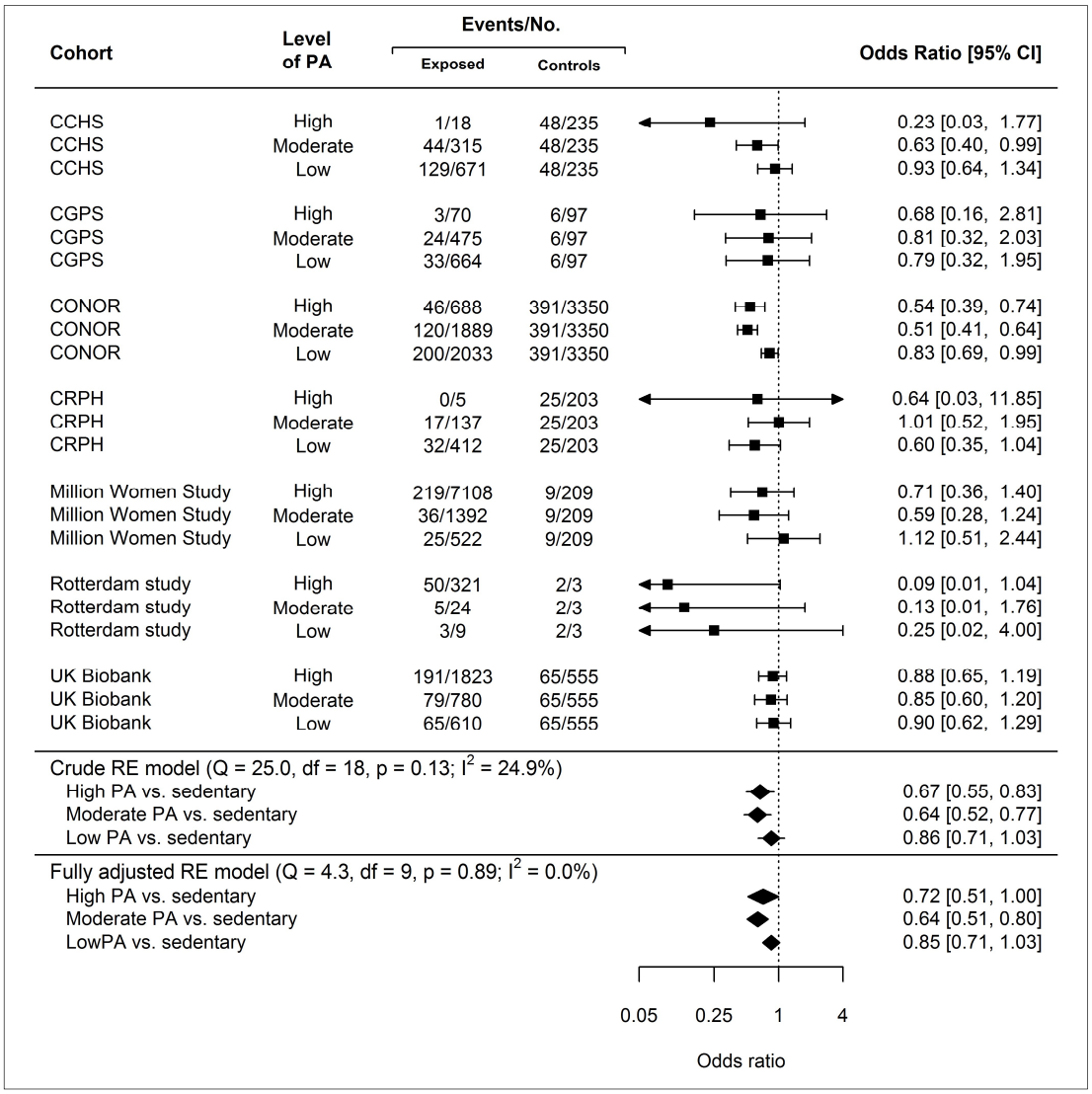


Figure 2 Forest plot for instant fatal myocardial infarction, by exposure contrast using sedentary as reference




The fully adjusted RE model was adjusted for age, sex, diabetes mellitus, arterial hypertension, family history of CVD, smoking, BMI, total blood cholesterol level, alcohol consumption and socioeconomic status.
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




The fully adjusted RE model was adjusted for age, sex, diabetes mellitus, arterial hypertension, family history of CVD, smoking, BMI, total blood cholesterol level, alcohol consumption and socioeconomic status.

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.