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Prognostic impact of physical activity prior to myocardial infarction: Case fatality and subsequent risk of heart failure and death

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Abstract

Background: Animal studies indicate that exercise reduces myocardial damage during myocardial infarction by ischaemic preconditioning.

Aim: To determine from a prospective cohort study whether the level of leisure time physical activity (LTPA) in humans prior to myocardial infarction could modify the course of myocardial infarction by reducing case fatality and the subsequent risk of heart failure and mortality.

Methods: A total of 14,223 participants in the Copenhagen City Heart Study were assessed at baseline in 1976–1978; 1,664 later developed myocardial infarction (mean age at myocardial infarction 70.9 years) and were followed through registries until 2013. We explored the association of LTPA assessed before myocardial infarction with the risk of fatal myocardial infarction, heart failure and all-cause mortality after myocardial infarction. Odds ratios (ORs) and hazard ratios (HRs) were estimated by logistic and Cox proportional hazards regression models, adjusted for age at myocardial infarction and other potential confounders.

Results: A total of 425 (25.5%) myocardial infarctions were fatal. Higher levels of LTPA prior to myocardial infarction were associated with lower case fatality: adjusted ORs (95% confidence interval), with reference to sedentary LTPA were 0.68 (0.51–0.89) for light LTPA and 0.53 (0.38–0.74) for moderate/high LTPA. A total of 360 (29.1%) of the 1,239 myocardial infarction survivors developed heart failure and 1,033 (83.4%) died during follow-up. There was no association between LTPA levels prior to myocardial infarction and the risk of heart failure or all-cause mortality after non-fatal myocardial infarction: adjusted HRs for moderate/high versus sedentary LTPA were 1.06 (0.78–1.45) and 0.90 (0.74–1.08), respectively.

Conclusion: Individuals who were physically active had lower case fatality of myocardial infarction, but survivors were not protected against subsequent heart failure or mortality.

Keywords

Physical activity, exercise training, ischaemic preconditioning, myocardial infarction, heart failure, prospective study

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Introduction

Regular physical activity is associated with a reduced risk of ischaemic heart disease (IHD) and mortality. Mechanisms are partly through beneficial effects on a number of cardiovascular risk factors, i.e. physical activity reduces blood pressure, improves dyslipidaemia, regulates body weight, improves insulin sensitivity

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and have a plethora of other beneficial effects.[1–3] Physical activity has also been shown to reduce the risk of developing heart failure[4] and one mechanism may be through ischaemic preconditioning.

One of the strategies to protect the heart from ischaemic injury is ischaemic preconditioning triggered by brief episodes of ischaemia. Several studies have found that ischaemic reperfusion injury is reduced by brief episodes of ischaemia during primary percutaneous coronary intervention (PCI) or before PCI by inflating a cuff around an arm.[5–8] In addition, patients with pre-infarction angina have smaller infarct size than patients without angina.[9] The mechanism seems to be through repeated ischaemia stimulating factors including the formation of collaterals and release of chemical substances which improve blood flow and reduce ischaemic reperfusion injury.[5,9–12] Animal studies have shown that exercise training of rats prior to an occlusion of a coronary artery can reduce the size of the infarction.[9,10,13–15] In animal studies, exercise training was also associated with a lower risk of heart failure, reduced arrhythmia, decreased myocardial stunning and improved coronary vascular reactivity in hearts exposed to ischaemia reperfusion.[9,10]

If we assume that a high level of physical activity causes repeated ischaemia in a patient with coronary artery disease, physical activity could result in protection of the myocardium and lead to smaller infarcted areas if a myocardial infarction (MI) develops. Smaller MIs could in turn reduce case fatality and the subsequent risk of heart failure and death.

The aim of this study was therefore to determine from a prospective cohort study whether the level of leisure time physical activity (LTPA) prior to the event modifies the prognosis after MI by reducing case fatality and the subsequent risk of heart failure and death.

Methods

Study population

The study was based on the Copenhagen City Heart Study, a prospective cardiovascular study of women and men aged 20–93 years randomly drawn from the Danish civil registration system residing in the east of Copenhagen.[16–18] The study was performed in 1976–1978 and included 14,223 participants (response rate 74%). Participants filled in self-reported questionnaires on general health, diseases, lifestyle and family history of IHD, a clinical examination was performed and non-fasting blood tests were drawn.[19]

Inclusion criteria. Participants who suffered a MI (International Classification of Diseases (ICD) 8th revision code 410 and ICD-10 codes I21–I22) after study inclusion and before 30 April 2013 were identified by linkage to the Danish National Patient Registry (NPR).

Exclusion criteria. Participants with self-reported or registry-based MI ($n = 433$) or stroke ($n = 50$) prior to study inclusion were excluded. Furthermore, participants with missing information on LTPA ($n = 3$) or diagnosed with heart failure before MI ($n = 328$) were also excluded. The study population thus consisted of 1,664 participants with MI (Figure 1).

The participants voluntarily participated in the Copenhagen City Heart Study and informed consent was obtained. The ethics committee for the Copenhagen area approved the study (V. 100.2039/91).

Baseline data

The following variables were registered at baseline in 1976–1978: age, gender, marital status, education (<8, 8–10 and >10 years, corresponding to lower primary school, higher primary school and secondary school), household income (low, medium and high), smoking (current, none), alcohol (abstainers, monthly/weekly and daily intake), body mass index (BMI), non-fasting plasma total cholesterol and triglycerides, self-reported diabetes, heart rate (bpm), systolic blood pressure (mmHg), treatment of hypertension, lung function, family history of IHD, angina pectoris and atrial fibrillation. Heart rate and atrial fibrillation were derived from ECG.

Systolic blood pressure was measured in the sitting position after 5 minutes of rest. BMI was calculated from the weight (kg) divided by height squared (m^2). Lung function was measured by electronic spirometer and chronic obstructive pulmonary disease was defined as forced expiratory volume at one second divided by forced vital capacity less than 0.70.[19]

Leisure time physical activity

The primary exposure variable LTPA at baseline was assessed by the Copenhagen City Heart Study leisure time physical activity questionnaire.[20,21] Participants graduated their LTPA during the last year into four levels: (a) Sedentary: almost completely sedentary or only light physical activity less than 2 hours/week (e.g. reading, television, cinema); (b) Light LTPA: 2–4 hours/week (e.g. walking, cycling, light gardening); (c) Moderate LTPA: Over 4 hours/week or 2–4 hours of more vigorous LTPA (e.g. brisk walking, fast cycling); (d) High LTPA: vigorous LTPA more than 4 hours/week or regular hard training or competitive sport

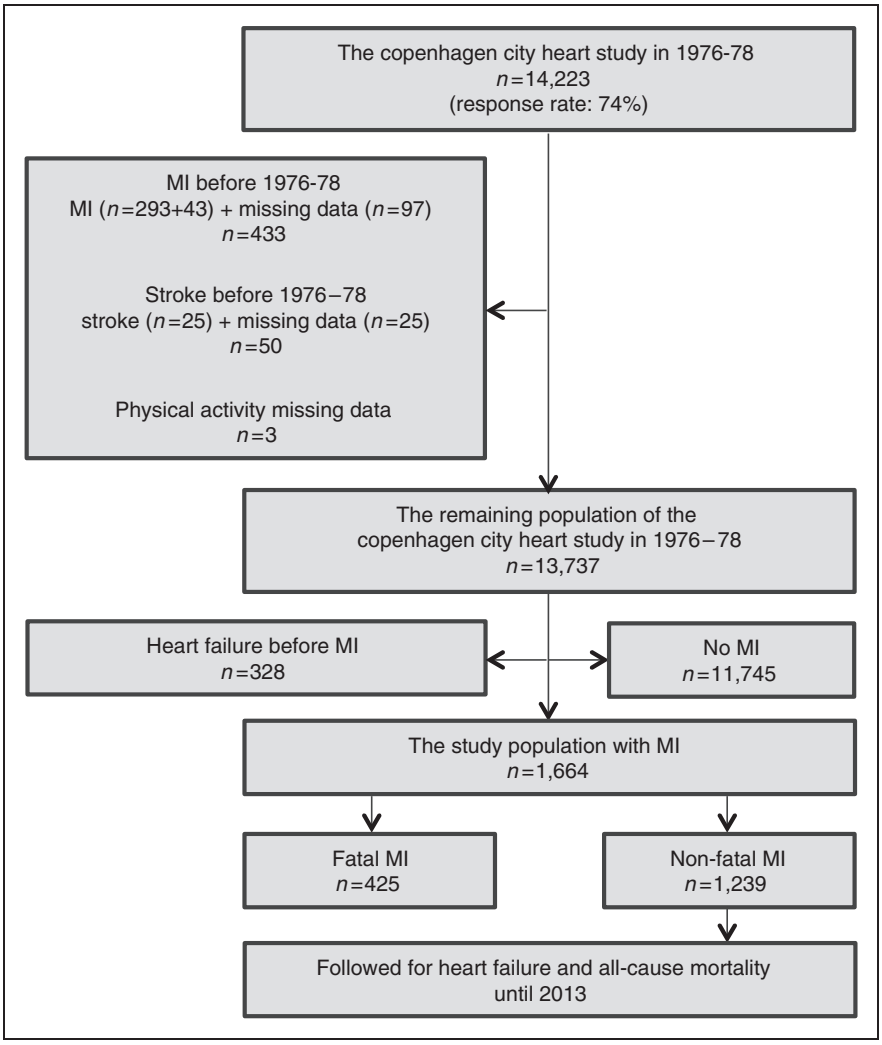

Figure 1. Flowchart of the study population with myocardial infarction (MI) from 1976 to 2013.

several times a week. To avoid inadequate group sizes moderate LTPA and high LTPA were merged.

Endpoints and follow-up

The primary endpoints were fatal versus non-fatal MI, and for non-fatal MI subsequent first hospital admission with heart failure or death. Heart failure was ascertained from the NPR and defined as ICD-8 codes 425.99, 427.09–427.11, 427.19 and 428.99 until 1 January 1994 and as ICD-10 codes I11.0, I25.5, I42.0, I42.6, I42.9, I50.0–9 from 1994 and onwards. Death after MI was identified through the Danish Cause of Death Register until March 2013. Participants diagnosed with non-fatal MI were followed until they developed an endpoint, emigration (automatic censoring ~0.1%), or end of follow-up (April 2013), whichever came first.

Statistical analysis

Baseline characteristics of the three LTPA levels were analysed by using the chi-squared test for categorical data and one-way analysis of variance (ANOVA) for continuous data. We used logistic regression to examine the association between LTPA and MI (fatal vs. non-fatal) in a model adjusted for age, gender, alcohol, smoking, hypertension treatment and education. We used Cox proportional hazard regression to examine any association between LTPA and heart failure and all-cause mortality after MI, in separate models, adjusted for age, gender, alcohol, smoking, hypertension treatment and education The follow-up began on the date of MI and continued until the date of diagnosis of heart failure or death, emigration, or 21 March 2013, whichever came first. Calendar time since date of MI was used as the

underlying time scale and all models were adjusted for age at the time of MI as a continuous variable. All the variables listed in Table 1 were considered as potential confounders, and only those associated with the outcome (P value <0.10) were included in the logistic and Cox regression model. Education and income are highly correlated. As income may not reflect socioeconomic status in the elderly, education was chosen as the indicator of socioeconomic status in the model. The chi-square test and ANOVA were performed using SPSS version 22.0, odds ratios (ORs) with 95% confidence intervals (CIs) were estimated with logistic function, whereas hazard ratios (HRs) and 95% CIs were estimated with *stcox* function, in Stata 13.1.

We checked the proportional hazards assumption by testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals on functions of time, and found no violations.

MI could occur up to several decades (up to 2013) after information on LTPA was gathered at the recruitment in 1976–1978 and might not reflect the LTPA at the time of the MI. To investigate whether LTPA reported close to the date of MI was more strongly associated with outcome, we conducted sensitivity analyses stratified and adjusted by MI occurring over or 10 years or less after baseline. Furthermore, between 1977 and 2013 treatment of MI including secondary prevention has changed substantially. To take this into account we adjusted for calendar time divided into following categories: 1976–1985, 1986–1995, 1996–2005 and 2006–2013.

Results

Baseline data

A total of 1,664 participants developed MI during follow-up, 979 (58.8%) men and 685 (41.2%) women. The median time from baseline to MI was 14.6 years and the mean age at MI was 70.9 years (SD $\pm$ 10.6) (Table 1). The majority of the participants had previously reported to practise light LTPA (54.0%). A larger proportion of the men reported moderate/high LTPA. There were only minor differences in age at MI between the LTPA groups. The main differences with LTPA was seen in socioeconomic variables, smoking, alcohol, hypertension and lung function, where the more physically active had a slightly more beneficial profile, whereas there was no difference between LTPA groups for the other cardiovascular risk factors normally associated with physical activity: diabetes, BMI, systolic blood pressure and cholesterol.

LTPA and fatal versus non-fatal MI

A total of 425 (25.5%) of 1,664 MIs were fatal immediately after MI onset. There was a dose-dependent association between LTPA and fatal MI. The ORs and 95% confidence intervals of fatal versus non-fatal MI for light physical activity were 0.68 (0.51–0.89) and for moderate/high physical activity 0.53 (0.38–0.74). The association was not affected by multivariable adjustment (Table 2).

LTPA and risk of heart failure after MI

The baseline characteristics of the 1239 participants who suffered a non-fatal MI were similar to those of the overall cohort and are presented in the supplementary material (Supplementary Table 1). During a mean 5.6 years of follow-up, and a total of 7355 person-years, 360 (29.1%) MI survivors developed heart failure, yielding an incidence rate of 48.9 per 1000 person-years. There was no statistically significant association between the three LTPA levels and the risk of heart failure, whether unadjusted or multivariable adjusted (Table 3). Results were similar in analyses adjusted and stratified by time from baseline to MI and adjustment for calendar time.

LTPA and mortality risk of death from all causes after MI

Of 1,239 MI survivors, 1,033 (83.4%) patients died during a mean follow-up of 6.9 years (min 0, max 33.8 years), giving a total of 8553 person-years of follow-up, and a mortality rate of 121 per 1000 person-years. There was no significant difference in mortality rate with levels of LTPA: after multivariable adjustment the HRs for light and moderate/high LTPA were 0.89 (0.76–1.05) and 0.90 (0.74–1.08), respectively. Results were similar in analyses adjusted and stratified by time from baseline to MI and adjustment for calendar time (Table 3).

Discussion

The main finding of this study was that patients who suffered a MI and were physically active prior to their MI were more likely to survive the event. We detected a dose–response association with decreasing risk of dying of MI immediately with increasing levels of physical activity, which was highly significant. Conversely, the study did not confirm the hypothesis that LTPA could offer protection against the subsequent development of heart failure and found only a small and insignificant reduction in premature mortality.

A wealth of literature has documented the beneficial effects of exercise on the risk of MI and mortality. The main effects of exercise are seen already at low to moderate levels, as reflected in the recommendations of current prevention guidelines.[22] However, to the best of

Table 1. Baseline characteristics of the participants with MI at the three LTPA levels, Copenhagen City Heart Study in 1976–1978.

Characteristics	Total $n = 1664$ (100)	Sedentary physical activity $n = 346$ (20.8)	Light physical activity $n = 898$ (54.0)	Moderate/high physical activity $n = 420$ (25.2)	*P* value
Sociodemographics					
Age at MI (years)	70.9 (±10.6)	70.0 (±10.5)	71.4 (±10.5)	70.7 (±10.6)	0.08
Gender					
Women	685 (41.2)	145 (41.9)	404 (45.0)	136 (32.4)	< 0.001
Marital status					
Live with a partner	1285 (77.2)	253 (73.1)	700 (78.0)	332 (79.0)	0.11
Education[a]					
Low primary school <8 years	886 (53.3)	216 (62.4)	460 (51.2)	210 (50.1)	0.001
High primary school 8–10 years	592 (35.6)	103 (29.8)	322 (35.9)	167 (39.9)	
Secondary school >10 years	185 (11.1)	27 (7.8)	116 (12.9)	42 (10.0)	
Household income[a]					
Low	429 (26.6)	118 (35.1)	226 (26.1)	85 (20.7)	<0.001
Medium	896 (55.5)	175 (52.1)	468 (54.0)	253 (61.6)	
High	288 (17.9)	43 (12.8)	172 (19.9)	73 (17.8)	
IHD risk factors					
Smoker					
Current	1180 (70.9)	263 (76.0)	626 (69.7)	291 (69.3)	0.06
Alcohol					
Abstainers	636 (38.2)	151 (43.6)	335 (37.3)	150 (35.7)	0.01
Monthly/weekly	568 (34.1)	90 (26.0)	328 (36.5)	150 (35.7)	
Daily intake	460 (27.6)	105 (30.3)	235 (26.2)	120 (28.6)	
BMI (kg/m^2)[a]	25.9 (±4.0)	26.0 (±4.3)	25.9 (±4.0)	25.9 (±3.6)	0.94
Total cholesterol (mmol/L)	6.5 (±1.2)	6.5 (±1.4)	6.5 (±1.2)	6.4 (±1.2)	0.16
Total triglyceride (mmol/L)	2.1 (±1.3)	2.1 (±1.3)	2.0 (±1.3)	2.1 (±1.3)	0.82
Diabetes	53 (3.3)	11 (3.3)	30 (3.5)	12 (3.0)	0.89
Heart rate (bpm)	74 (±13)	75 (±14)	75 (±13)	74 (±13)	0.55
Systolic blood pressure (mmHg)	142.5 (±22.1)	141.9 (±21.6)	142.8 (±22.4)	142.2 (±22.2)	0.17
Treated hypertension	135 (8.1)	32 (9.2)	83 (9.3)	20 (4.8)	0.01
COPD	79.1 (±10.4)	77.6 (±11.3)	79.1 (±10.2)	80.1 (±9.9)	0.04
Family history of IHD	624 (37.5)	126 (36.4)	356 (39.6)	142 (33.8)	0.11
Angina pectoris	594 (35.7)	128 (37.0)	328 (36.6)	138 (32.9)	0.36
Atrial fibrillation	119 (7.2)	21 (6.1)	64 (7.1)	34 (8.1)	0.56
Outcomes					
Fatal MI	425 (25.5)	111 (32.1)	227 (25.3)	87 (20.7)	0.002
Non-fatal MI	1239 (74.9)	235 (67.9)	671 (74.7)	333 (79.3)	
Heart failure	360 (21.6)	67 (19.4)	187 (20.8)	106 (25.2)	0.10
Died	1458 (87.6)	315 (91.0)	791 (88.1)	352 (83.8)	0.01

MI: myocardial infarction; LTPA: leisure time physical activity; BMI: body mass index; IHD: ischaemic heart disease; COPD: chronic obstructive lung disease.

Analysed with chi-square test or one-way analysis of variance test. Values were represented in *n* (%) or mean (±SD).

[a]Missing data, therefore total not $n = 1,664$.

our knowledge, the issue of whether exercise reduces case fatality in MI has not previously been addressed in prospective studies.

The existing literature suggests that ischaemic preconditioning seems to reduce myocardial damage after MI,[10,15] and we therefore hypothesised that individuals suffering from a MI with a habitual moderate/high level of LTPA have some degree of cardioprotection, manifested in lower MI case fatality rates, smaller myocardial infarct size and subsequently a reduced risk of

Table 2. LTPA and odds of case fatality from MI in 1,664 participants from Copenhagen City Heart Study who developed MI between 1976 and 2013.

	OR (95% CI)		
	Sedentary physical activity	Light physical activity	Moderate/high physical activity
Case fatality ($n = 425$)			
Model 1 (A): age	1.00	0.68 (0.51–0.89)	0.53 (0.38–0.74)
Model 2 (B): age and gender	1.00	0.68 (0.51–0.89)	0.52 (0.37–0.72)
Model 3 (C): fully[a] adjusted	1.00	0.70 (0.53–0.92)	0.55 (0.39–0.76)

MI: myocardial infarction; LTPA: leisure time physical activity; OR: odds ratio; CI: confidence interval.
[a]Age, gender, alcohol, smoking, hypertension treatment, education.

Table 3. LTPA and risk of heart failure and all-cause mortality after MI in 1,239 participants from Copenhagen City Heart Study between 1976 and 2013.

	HR (95% CI)		
	Sedentary physical activity	Light physical activity	Moderate/high physical activity
Heart failure ($n = 360$)			
Model 1 (A): age	1.00	0.84 (0.64–1.12)	1.07 (0.79–1.45)
Model 2 (B): age and gender	1.00	0.84 (0.64–1.12)	1.07 (0.78–1.45)
Model 3 (C): fully[a] adjusted	1.00	0.85 (0.64–1.12)	1.06 (0.78–1.45)
Sensitivity analyses 1[b]	1.00	0.85 (0.64–1.12)	1.07 (0.78–1.46)
Sensitivity analyses 2[c]	1.00	0.85 (0.64–1.12)	1.07 (0.78–1.46)
All-cause mortality ($n = 1,033$)			
Model 1 (A): age	1.00	0.86 (0.73–1.01)	0.86 (0.71–1.03)
Model 2 (B): age and gender	1.00	0.86 (0.73–1.00)	0.84 (0.70–1.01)
Model 3 (C): fully[a] adjusted	1.00	0.89 (0.76–1.05)	0.90 (0.74–1.08)
Sensitivity analyses 1[b]	1.00	0.89 (0.76–1.05)	0.88 (0.73–1.06)
Sensitivity analyses 2[c]	1.00	0.89 (0.76–1.05)	0.90 (0.74–1.07)

MI: myocardial infarction; LTPA: leisure time physical activity; HR: hazard ratio; CI: confidence interval.
[a]Age, gender, alcohol, smoking, hypertension treatment, education.
[b]Age, gender, alcohol, smoking, hypertension treatment, education, MI $>$ or $\leq$10 years.
[c]Age, gender, alcohol, smoking, hypertension treatment, education, MI calendar time.

heart failure and mortality after MI. We found a dose–response association and a significant (45%) lower risk of fatal MI in those with a moderate/high level of LTPA compared to those with sedentary LTPA. The association was not attenuated by multivariable adjustment or after a series of sensitivity analyses. However, given the wide range of time lapse from measurement of LTPA to the development of MI, participants may have changed their exercise habits as well as other risk factors considerably. Whether ischaemic preconditioning plays a causal role in the association remains speculative at present.

Conversely, we did not find any protective effect of LTPA on the subsequent development of heart failure following MI. This might be related to the lower case fatality among those with higher LTPA. If the sedentary have larger infarctions and thus higher case fatality, among the MI survivors, habitual exercise may no longer be associated with the infarction size and consequently the risk of subsequent heart failure might be similar. However, other explanations include that this was a relatively small study and the statistical power was limited, as reflected in the wide CIs ranging from 36% reduced risk to 45% increased risk. As mentioned above, changes in LTPA prior to MI may also have attenuated associations. A previous study from the Copenhagen City Heart Study showed that participants who decreased the LTPA level at least one or two levels had a higher risk of ischaemic heart disease and MI.[23] If the participants in this study changed their LTPA

from a moderate/high to a sedentary level between the baseline assessment and their MI, it must be assumed that the risk of cardiovascular disease increased and the effect of preconditioning diminished. This limitation was addressed by stratifying analyses by year lag-time from baseline information to MI. However, these yielded similar results. Unfortunately, we did not have information on the size of infarction either from the maximum rise in coronary markers of necrosis or in left ventricular ejection fraction. Furthermore, lifestyle changes including exercise habits after the MI are also likely to play a role in prognosis. In summary, larger studies and studies that take physical activity after the MI into account are needed to determine whether physical activity confers any protection against the development of heart failure in the post-MI setting.

Strengths and limitations

The strengths of the study include the prospectively recorded exposure information, permitting adjustment for several important potential confounders; the relatively large sample size; and the use of national registries with complete information which minimises attrition bias.[18] In the past 40 years the way of diagnosing and treating MI and heart failure has changed. The adjustment for calendar time ensures that findings are not spuriously caused by changes in outcome after MI in the recent decades. The outcome registry initially included only hospital admission, but since 1995 outpatient diagnoses were included.[24] In order to examine whether temporal trends in underlying risk or management of disease or in the type of data registered may have biased results, we re-analysed data in four separate time periods and we also adjusted for year of suffering the MI. Results were similar in these sensitivity analyses.

Another limitation of the study is that LTPA was self-reported and assessed rather crudely, in four predefined categories. Over half (54%) of the participants have classified themselves as doing light LTPA. Survey participants have a tendency to rate themselves in the middle of a scale or possibly they respond to what they find socially appealing (social desirability).[25] There is therefore a risk of misclassification, which may give rise to bias. Further limitations include the lack of information on the size of infarction and of left ventricular ejection fraction at the time of MI and the time elapsed between baseline data and the date of MI, as discussed above.

Conclusion

Whether exercise reduces myocardial damage during MI by ischaemic preconditioning in humans has to our knowledge not been tested before. This study shows that higher levels of LTPA prior to MI were associated with a lower risk of fatal MI, but did not affect the risk of subsequently developing heart failure and death after MI. The findings may prove important for future recommendations on LTPA, but need to be confirmed in larger prospective studies.

Author contribution

Conceived and designed the study: HE, EP, MCEC. Performed the study: HE, EP, MCEC. Analysed the data: HE, EP, ZJA. Wrote the paper: HE. Data research and contributed to discussion, reviewed and edited the manuscript: HE, EP, PS, MCEC, PPJ and ZJA.

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Declaration of conflicting interests

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