Dose–response association of physical activity with acute myocardial infarction: Do amount and intensity matter?

Roberto Elosua a,b,⁎, Ana Redondo a, Antonio Segura c, Miquel Fiol d,e, Elena Aldasoro b,f, Gema Vega g, Jordi Fortezad, Helena Martí a, José María Arteagoitia f, Jaume Marrugat a

a Grupo de Epidemiología y Genética Cardiovascular, IMIM (Institut Hospital del Mar d’Investigacions Mèdiques), Barcelona, Spain
b CIBER Epidemiología y Salud Pública, Barcelona, Spain
c Instituto de Ciencias de la Salud de Castilla-La Mancha, Talavera de la Reina, Spain
d CIBER Obesidad y Nutrición, Palma de Mallorca, Spain
e Departamento de Sanidad, Gobierno Vasco, Vitoria-Gasteiz, Spain
f Unidad de Cuidados Intensivos, Complejo Hospitalario, Albacete, Spain

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Abstract

Objective. The aims of this study were to analyze the dose–response association between leisure time physical activity (PA) practice and myocardial infarction (MI), considering not only the total amount but also the amount of PA at different levels of intensity, and to determine whether these associations were modified by age.

Method. In a population-based age- and sex-matched case–control study, all first acute MI patients aged 25 to 74 years were prospectively registered in four Spanish hospitals between 2002 and 2004. Controls were randomly selected from population-based samples recruited during the same period of time. The Minnesota PA questionnaire was administered to assess total energy expenditure in PA and in light-, moderate-, and high-intensity PA.

Results. Finally, 1339 cases and 1339 controls were included. The association between PA and MI likelihood was non-linear, with significantly lower MI odds at low practice levels (≥500 MET·min/week), lowest odds around 1500 MET·min/week, and a plateau thereafter. Light- (in subjects older than 64 years), moderate-, and high-intensity PA produced similar benefits.

Conclusion. Most of the population could reduce their likelihood of MI by engaging in PA at a moderate level of intensity or, in individuals older than 64 years, at a light level of intensity.
Methods

Study design

A large population-based age- and sex-matched case–control study was conducted in four areas of Spain. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, it was approved by the local ethics committee, and all the participants gave informed consent.

Identification of cases

All first acute MI patients aged 25 to 74 years admitted to coronary care units in the participating hospitals during the study period (June 2002 to May 2004) were prospectively registered for the study based on international World Health Organization criteria (Gillum et al., 1984); acute MI was diagnosed when two or more of the following criteria were present: abnormal new Q waves, increase in cardiac enzymes beyond twice the upper normal value, and chest pain lasting more than 20 min. All the patients included in this study were interviewed during a hospital stay by trained nurses using standardized methods and questionnaires (Baena-Díez et al., 2009).

Selection of controls

Controls were age- (±2 years) and sex-matched with cases and were randomly selected from population-based samples recruited from the same population origin as the cases, in the same time period, using data from the National Census (http://www.ine.es/inebmenu/mnu_cifrasprp.htm). They were ineligible if they had presented a previous MI. Participation rate in these surveys was superior to 70%.

Physical activity assessment

The amount and intensity of PA performed during the previous year were assessed by the Minnesota leisure time PA questionnaire. This questionnaire has been described elsewhere (Taylor et al., 1978) and has been validated for use among Spanish men and women (Elosua et al., 1994, 2000). A score reflecting total energy expenditure in PA (total EEPA) in leisure time was obtained, the unit used to quantify the amount of PA was MET·min/week (Jacobs et al., 1993). Moreover, three energy expenditures in leisure time PA, according to their intensity code, were also estimated: light intensity (<4 METs), moderate intensity (4–5.9 METs), and high intensity (≥6 METs). Thus, for each participant:

Total $\text{EEPA} = \text{energy expenditure in light intensity PA} + \text{energy expenditure in moderate intensity PA} + \text{energy expenditure in high intensity PA}$

Other variables

Subjects were classified as current cigarette smokers if they reported having smoked at least one cigarette/day during the previous year. Hypertension, diabetes, and dyslipidemia were recorded on the basis of self-report diagnosis or use of prescribed medications using MONICA standardized questionnaires (Baena-Díez et al., 2009).

Statistical methods

The differences between cases and controls were analyzed using Chi-square tests for categorical variables and Student t-test or Mann–Whitney U test for continuous variables. The differences between participants across defined PA groups were analyzed by Chi-square and ANOVA linear test.

Conditional logistic regression was used in the multivariate analysis to determine the adjusted association of PA practice with MI. Furthermore, non-parametric generalized additive models (Cadasso-Suarez et al., 2005; Figueiras and Cadasso-Suarez, 2001) to study the dose–response relationship between PA and MI likelihood were used. The best-fitted parsimonious non-parametric model describing the relation between PA and MI was selected based on the minimum Akaike Information Criterion. PA practice was considered as a continuous variable after assigning the individuals to different PA practice levels (0–99, 100–199, 200–299, ... MET·min/week). Two distinct models, one for total EEPA and the other concurrently including energy expenditure in light, moderate, and high intensity PA, were defined and adjusted for age, sex, smoking, hypertension, diabetes and dyslipidemia.

The analyses were also stratified by age (25–64 and 65–74 years). A two-tailed p-value < 0.05 was considered statistically significant.

Results

During the study period, 1864 acute MI patients were prospectively registered in the participating hospitals. Of these, 1346 (72.9%) had valid data for the variable PA. Those with PA data were younger and had a lower prevalence of diabetes and hypertension than those not included because of missing PA data. We excluded 7 cases for lack of an age- and sex-matched control. Finally, 1339 cases and 1339 controls matched for age and sex were included in the analysis.

The main characteristics of cases and controls included in the study are presented in Table 1. The prevalence of smoking, hypertension, dyslipidemia, and diabetes was higher in cases than in controls. Controls reported higher EEPA than cases, regardless of PA intensity.

Total physical activity practice and myocardial infarction odds

The characteristics of the participants across the 8 defined groups according to total EEPA are presented in Table 2. Briefly, the higher the total EEPA, the higher the age and the lower the prevalence of smoking, hypertension, and dyslipidemia and the proportion of women. The multivariate adjusted odds ratios across total EEPA groups for MI, obtained by conditional logistic regression, are also shown in Table 2: total EEPA between 500 and 1000 MET·min/week was associated with lower odds of MI compared with a total EEPA lower than 500 MET·min/week. Further increases in total EEPA were also associated with lower MI odds, although the magnitude of the odds reduction was similar.

The results of the non-parametric regression methods were similar, the decline in MI likelihood was greatest at low levels of EEPA and diminished in magnitude as EEPA increased, achieving the lowest odds ratios around 1500 MET·min/week, with a plateau thereafter (Fig. 1-A).

Similar results were obtained when the analyses were stratified by age groups.

Light-intensity physical activity practice and myocardial infarction odds

Energy expenditure in light-intensity PA was directly associated with age and the prevalence of diabetes and inversely associated with the prevalence of smoking (Supplementary Table 1). In the conditional

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and energy expenditure in physical activity of cases and controls included in the study. Population-based controls and consecutive patients from four Spanish hospitals recruited in 2002–2004.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases n = 1339</td>
<td>Controls n = 1339</td>
</tr>
<tr>
<td>Age (years)�</td>
<td>61.1 (10.7)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>302 (22.6)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>565 (44.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>709 (54.3)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>681 (53.7)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>360 (27.9)</td>
</tr>
<tr>
<td>Total $\text{EEPA}^\text{a}$ (MET·min/week)</td>
<td>1242 (311; 2757)</td>
</tr>
<tr>
<td>EE Light $\text{PA}^\text{a}$ (MET·min/week)</td>
<td>432 (0; 1470)</td>
</tr>
<tr>
<td>EE Moderate $\text{PA}^\text{a}$ (MET·min/week)</td>
<td>0 (0; 645)</td>
</tr>
<tr>
<td>EE High $\text{PA}^\text{a}$ (MET·min/week)</td>
<td>56 (0; 189)</td>
</tr>
</tbody>
</table>

= Total $\text{EEPA}$: Total energy expenditure in physical activity; = Energy expenditure in light-intensity physical activities (<4 METs); = Energy expenditure in moderate-intensity physical activities (4–5.5 METs); = Energy expenditure in high-intensity physical activities (6–14 METs).

= Mean (standard deviation), p-value estimated with the Student t-test.

= Median (percentile 25; percentile 75), p-value estimated with the Mann–Whitney U test.
logistic regression analysis, energy expenditure in light-intensity PA between 500 and 1499 MET·min/week was significantly associated with lower odds of MI; when energy expenditure in this type of PA was higher than 1499 MET·min/week, the association with MI likelihood was not statistically significant and tended to disappear (Supplementary Table 1).

In the non-parametric regression, a similar association pattern was observed (Fig. 1-B).

Table 2

<table>
<thead>
<tr>
<th>Total energy expenditure in physical activity (MET·min/week)</th>
<th>Linear trend p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–499</td>
<td>n = 590</td>
</tr>
<tr>
<td>500–999</td>
<td>n = 373</td>
</tr>
<tr>
<td>1000–1499</td>
<td>n = 345</td>
</tr>
<tr>
<td>1500–1999</td>
<td>n = 299</td>
</tr>
<tr>
<td>2000–2499</td>
<td>n = 223</td>
</tr>
<tr>
<td>2500–2999</td>
<td>n = 182</td>
</tr>
<tr>
<td>3000–3499</td>
<td>n = 121</td>
</tr>
<tr>
<td>≥3500</td>
<td>n = 545</td>
</tr>
<tr>
<td>Age (years) (a)</td>
<td>59.6 (11.2)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>29.8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>40.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>50.6</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>49.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24.2</td>
</tr>
<tr>
<td>Cases (%)</td>
<td>69.2</td>
</tr>
<tr>
<td>Odds ratio (95% confidence interval) (b)</td>
<td>1</td>
</tr>
</tbody>
</table>

\(a\) Mean (standard deviation); ANOVA.

\(b\) Adjusted for smoking, hypertension, dyslipidemia, and diabetes (age- and sex-matched).

Fig. 1. Dose–response association pattern for energy expenditure in physical activity and myocardial infarction odds: total energy expenditure (panel A), energy expenditure in light-intensity physical activity (panel B), energy expenditure in moderate-intensity physical activity (panel C), and energy expenditure in high-intensity physical activity (panel D). Population-based controls, and consecutive patients from four Spanish hospitals, recruited in 2002–2004.
When the analyses were stratified by age, an inverse association between light PA and MI was observed in participants older than 64 years (Fig. 2-B) but not in younger subjects (Fig. 2-A); the interaction between age and light PA was statistically significant (p-value = 0.0018).

**Moderate-intensity physical activity practice and myocardial infarction odds**

Energy expenditure in moderate-intensity PA was directly associated with age and inversely associated with hypertension, dyslipidemia, smoking and the proportion of women (Supplementary Table 2). In the logistic regression analyses, energy expenditure in moderate-intensity PA between 500 and 999 MET·min/week was associated with lower MI odds; further increases in energy expenditure in this type of PA were also associated with lower MI odds, although the magnitude of the association did not increase (Supplementary Table 2).

In the non-parametric regression, moderate-intensity PA practice was associated with lower MI odds; the lowest odds ratio was observed at 1000 MET·min/week, followed by a plateau (Fig. 1-C). Similar results were obtained when the analyses were stratified by age groups.

**High-intensity physical activity practice and myocardial infarction odds**

Energy expenditure in high-intensity PA was inversely associated with age, hypertension, dyslipidemia, diabetes and the proportion of women (Supplementary Table 3).

In the logistic regression analyses, energy expenditure in high-intensity PA greater than 100 MET·min/week was associated with lower MI odds (Supplementary Table 3).

In the non-parametric regression high-intensity PA was associated with lower MI likelihood, the lowest odds ratio was observed at 1000 MET·min/week followed by a plateau (Fig. 1-D). Similar results were obtained when the analyses were stratified by age groups.

**Discussion**

In this large population-based case–control study we report that the dose–response curve for the association between total PA practice and MI is non-linear, with a great reduction in MI odds at low PA doses and a modest reduction in the odds with increased PA practice until achieving a maximum point and then reaching a plateau. Moreover, when considering PA intensity, our data indicate that light-intensity PA (≤ 4 METs) is associated with lower MI odds in participants older than 64 years but not in younger ones; moderate (4–5.5 METs) and high (≥ 6 METs) intensity PA are associated with lower MI odds in the population aged 25 to 74 years.

Assessment of the dose–response association pattern for PA practice and MI is a key point to define health promotion policies that could enhance the public’s adherence to PA recommendations and promote broader compliance. We report that a total EEPA greater than 500 MET·min/week is sufficient to significantly lower MI likelihood, with lowest odds ratios observed at an energy expenditure corresponding to 1500 MET·min/week, with no further decreases in MI odds beyond this point.

These results are consistent with other studies assessing the relationship between PA practice and health, which have found that low PA doses are associated with great coronary (Sattelmair et al., 2011; Sesso et al., 2000; Sofi et al., 2008), cardiovascular (Sesso et al., 1999), and global health benefits (Lee and Paffenbarger, 2000). In patients with diabetes, an EEPA greater than 600 MET·min/week is associated with cardiovascular health benefits, with maximum benefits achieved by an EEPA ≈ 1200 MET·min/week (Di Loreto et al., 2005).

Sattelmair et al. (2011) recently published a meta-analysis of the dose–response association between PA and risk of CHD, reporting results similar to ours. They also reported a statistically significant interaction between sex and PA practice that reduced CHD risk, achieving a greater reduction in women than in men. This interaction was non-significant in our study, but the statistical power to detect such interaction in our sample was low. Altogether, these data reinforce the message that great benefits can be obtained with low levels of PA practice that could be achieved by most people.
More controversies exist when considering PA intensity and CHD risk (Swain and Franklin, 2006). In the Harvard alumni study (Sesso et al., 2000) and others (Folsom et al., 1997; Wagner et al., 2002; Wannamethee et al., 1998), the association between PA and reduced coronary risk was clear for high-intensity PA. In agreement with these findings, we report a significant association between this high level of PA and MI (Fig. 1-D), although the confidence intervals were very wide due to the limited practice of this type of activity in our population.

The association between moderate- and light-intensity physical activities and CHD is less consistent in the literature (Folsom et al., 1997; Sesso et al., 2000; Wagner et al., 2002; Wannamethee et al., 1998). In our study, we report an inverse association between moderate-intensity PA practice and MI odds, independent of age.

One of the most interesting and potentially important results of our study is the age-related difference in the association between light-intensity PA and MI: light-intensity PA was associated with lower MI odds only in older subjects. These results are concordant with other studies indicating that light-to-moderate-intensity physical activities, such as walking (Ainsworth et al., 2000), were associated with lower CHD rates (Gregg et al., 2003; Hakim et al., 1998), with a risk reduction similar to that of more vigorous physical activities (Lee et al., 2001; Manson et al., 2002; Noda et al., 2005). Interpretation of these results should also consider the differences between absolute and relative intensities according to age and fitness: moderate-intensity activity could be considered as light intensity by a young, fit individual and as high intensity by an older, less fit individual (Shephard, 2001). Individual perception of PA intensity, independent of the absolute intensity, has been associated with CHD risk in other studies (Lee et al., 2003).

Another potential explanation for the observed differences in the association between light intensity PA and MI could be related to the differences in the pathogenesis and mechanisms of MI at different ages. In the young population, familial hypercholesterolemia, smoking, and drug abuse could be more important than in the older population in which other factors such as hypertension and diabetes could play a greater role. Light intensity PA could also be differentially associated with this different risk factor profile.

All these results support current recommendations that the entire population should accumulate at least a weekly EEPA of 1000 kcal (Haskell et al., 2007; The National Physical Activity Plan, 2011; Vuori population should accumulate at least a weekly EEPA of 1000 kcal (3.5 METs). This supports the idea that increasing the practice of activity most of the light-intensity PA consisted of walking for pleasure intensity PA practice, at least in subjects older than 65 years. In our greater role. Light intensity PA could also be differentially associated with other factors such as hypertension and diabetes could play a more important than in the older population in which other factors such as hypertension and diabetes could play a greater role. Light intensity PA could also be differentially associated with this different risk factor profile.

All these results support current recommendations that the entire population should accumulate at least a weekly EEPA of 1000 kcal (Haskell et al., 2007; The National Physical Activity Plan, 2011; Vuori et al., 1999), although significant benefit could also be obtained with somewhat lower levels of PA practice. On the other hand, although current guidelines recommend moderate-intensity PA practice, a significant and quite similar benefit could be obtained with light-intensity PA practice, at least in subjects older than 65 years. In our study most of the light-intensity PA consisted of walking for pleasure (3.5 METs). This supports the idea that increasing the practice of activities such as walking is a good strategy to increase EEPA at the population level (Redondo et al., 2011; Westerterp, 2001).

Study strengths and limitations

One of the main strengths of the study is that the analyses were conducted in a large population-based sample: consecutive patient cases and controls were randomly selected from the same population base. It is important to note, however, that PA was a missing variable in a significant proportion of cases, most of them patients who died during the hospital stay without having completed the interview. These patients were older and had a higher prevalence of hypertension and diabetes, suggesting that this exclusion would lead to a conservative bias. Other limitations of the study include the retrospective design, the assessment of physical activity with a questionnaire that is based on self-reported information could introduce some measurement bias, although it had been previously validated. Moreover, work-related physical activity (modes of commuting, occupational and household tasks) and sedentary behavior were not considered. The generalizability of these results to other populations should be confirmed. Finally, these results should be replicated in prospective studies.

Conclusion

We defined the dose–response relationship between PA practice and MI and found significantly lower MI odds at low PA doses (100 to 499 MET-min/week), with lowest MI odds around 1500 MET-min/week, and a plateau thereafter. When PA intensity is considered, light-intensity PA practice is associated with lower MI odds in subjects older than 65 years; however, in younger individuals, at least moderate-intensity physical activity appears to be required to establish this association. Most of the population could achieve this PA practice level by walking at 3 miles/h (5 km/h) at least 140 min/week, which could reduce the odds of MI by 40% to 60%.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2013.07.022.

References


