

# Physical Activity and Cardiovascular Mortality Risk: Possible Protective Mechanisms?

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## ABSTRACT

**Introduction:** The biological mechanisms through which increased physical activity or structured exercise training lowers the risk of recurrent cardiac events are incompletely understood. We examined the extent to which modification of primary risk markers explains the association between physical activity and cardiovascular death in participants with diagnosed cardiovascular disease (CVD).

**Methods and Results:** In a prospective study of 1429 participants with physician-diagnosed CVD living in England and Scotland (age =  $66.5 \pm 11.1$  yr (mean  $\pm$  SD), 54.2% men), we measured physical activity and several risk markers (body mass index, total-to-HDL cholesterol ratio, diagnosed diabetes, systolic blood pressure, resting heart rate, C-reactive protein) at baseline. The main outcome was CVD death. There were a total of 446 all-cause deaths during an average of  $7.0 \pm 3.1$  yr of follow-up, of which 213 were attributed to cardiovascular causes. Participation in moderate to vigorous physical activity at least three sessions per week was associated with lower risk of CVD death (hazard ratio = 0.61, 95% confidence interval = 0.38–0.98). Physically active participants demonstrated significantly lower levels of body mass index, diabetes, and inflammatory risk (C-reactive protein). Metabolic (body mass index, total-to-HDL cholesterol ratio, and physician-diagnosed diabetes) and inflammatory risk factors explained an estimated 12.8% and 15.4%, respectively, of the association between physical activity and CVD death.

**Conclusions:** Physical activity may reduce the risk of secondary CVD events, in part, by improving metabolic and inflammatory risk markers.

The most recent and comprehensive meta-analysis concluded that structured exercise training improves survival and reduces recurrent events in coronary heart disease (CHD) patients (3). However, all randomized controlled trials considered were published before 2000, and participants were primarily middle-age, low-risk males with CHD. Supervised exercise training trials are considered the gold-standard experimental design to assess the efficacy of exercise in treating CHD. However, most programs are generally limited to 6 months followed by unsupervised physical activity with a mean follow-up of approximately 2.5 yr. Although susceptible to biases such as residual confounding, epidemiological cohort studies have the added advantage of following participants for longer periods of time to assess hard clinical end points. Few studies have prospectively examined the association of leisure time physical activity on mortality among participants with established CVD in a general population (2,5,8,9,12,22,25).

The British Regional Heart Study previously reported that the beneficial effects of physical activity and changes therein on 4-yr mortality rates were limited to light and moderate levels in males with a wide range of preexisting cardiovascular disease (CVD) (22). Data from the original Framingham Heart Study showed that moderate and high physical activity levels resulted in improved life expectancy of 1.3 and 3.7 yr, respectively, among participants with a history of CVD (5). Moreover, the biological mechanisms through which physical activity lowers the risk of recurrent events remain incompletely understood. Exercise training studies in cardiac patients demonstrate modest but consistent improvements in various risk factors, such as cardiac performance, aerobic capacity, endothelial function, and inflammatory markers (4,6,11,24). We recently demonstrated that inflammatory risk factors and blood pressure made the largest contribution to the inverse association between physical activity and CVD events in a healthy sample (7). However, limited prospective epidemiological data that have evaluated the influence of protective mechanisms underlying the relationship between physical activity and reduced CVD deaths exist in participants with preexisting CVD. Thus, the aim of this study was to further examine the association between moderate to vigorous leisure time physical activity and risk of CVD death in patients with diagnosed CVD. Second, we examined the extent to which cardiometabolic risk factors explain the association between physical activity and cardiovascular death in these participants.

## METHODS

### Study design and participants

Participants were recruited into the Health Survey for England and Scottish Health Survey, both representative, general population-based studies sampling individuals living in households in each country (18). Consenting study members (90% in Health Surveys for England, 82.5% in Scottish Health Surveys) were linked to National Health Service mortality data. Study participants gave full informed consent, and ethical approval was obtained from the London Research Ethics Council. At baseline, a total of 6271 participants reported physician-diagnosed ischemic heart disease or stroke (5.7% of the overall sample), although only 46.3% ( $n = 2903$ ) consented to a nurse visit. A further 1474 participants had missing demographic data; thus, the present analyses contained 1429 participants (age =  $66.5 \pm 11.1$  yr, 54.2% male). Excluded participants ( $n = 4842$ ) were older ( $68.0$  vs  $66.4$  yr,  $P < 0.001$ ) than those included, although there were no differences in sex distribution (47.4% vs 45.3% female,  $P = 0.15$ ), and the cardiovascular death rate was also similar (16.1% vs 14.6%,  $P = 0.16$ ).

## Demographic and clinical variables

Computer-assisted personal interviewing modules assessed respondents' demographics, health status and history of disease, and health behaviors (smoking and physical activity habits). Frequency of moderate to moderate-vigorous physical activities (MVPA) in the 4 wk before the interview, including sessions lasting for at least 30 min (walking and heavy domestic) or 15 min (recreational sports and structured exercise), was assessed. The definition of MVPA was based on activities greater than 3 METs (1). The validity of the physical activity questionnaire is supported by objective measures of activity using accelerometry devices in 106 British adults from the general population (10).

In a separate visit within a few days, qualified nurses recorded medication ([beta]-blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium blockers, lipid-lowering medications), measured height and body mass, collected blood samples, and measured seated blood pressure and resting heart rate (using an Omron HEM-907 [Omron Europe, Hoofddorp, The Netherlands] blood pressure monitor) three times after 5 min of rest in between each reading. Blood samples were analyzed for C-reactive protein (CRP) and total and HDL cholesterol. The analysis of CRP levels from serum was performed using the N Latex High-Sensitivity CRP mono immunoassay on the Behring Nephelometer II analyzer (Dade Behring, Newark, Germany). The limit of detection was  $0.17 \text{ mg}\cdot\text{L}^{-1}$ , and the coefficient of variation was <6%. Total and HDL cholesterol was measured using cholesterol oxidase assays on an Olympus 640 analyzer (Olympus, Center Valley, PA). Diabetes was ascertained from a self-reported physician's diagnosis.

## Mortality follow-up

Classification of the underlying cause of death was based on information collected from the death certificate together with any additional information provided subsequently by the certifying doctor. Diagnoses for primary cause of death were recorded using the International Classification of Diseases, 9th and 10th revisions. We used codes 390-459 (ICD-9) and I01-I99 (ICD-10) to identify cardiovascular death.

## Statistical analyses

MVPA was categorized into three groups corresponding to none, less than three sessions per week, and three or more per week. We used an ANOVA with Scheffe post hoc tests to examine the association between MVPA categories and CVD risk factors. The CRP data were log transformed to normalize the distribution. We used Cox proportional hazards models to compute hazard ratios (HR) with accompanying 95% confidence intervals (CI) for the association between MVPA and cardiovascular/all-cause death. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. In these analyses, calendar time (months) was the time scale. For participants who remained alive, the data were censored on February 28, 2008, in the Health Survey for England and December 30, 2008, in the Scottish Health Survey. To test the extent to which CVD risk factors account for the association between MVPA and cardiovascular death, we a priori grouped together CVD risk factors considered to be potential mediators. This included metabolic (body mass index, total-HDL cholesterol ratio, diabetes), cardiovascular (systolic blood pressure, resting heart rate), and inflammatory (CRP) risk factors. Because these risk factors are known to be associated with one another, all models were mutually exclusive of one another and also adjusted for other potential confounders including age, sex, smoking, and use of cardioprotective medication (yes/no). The percentage change in HR after multiple adjustments in comparison with the basic (age,

sex, smoking, and medication adjusted) model was quantified as follows:  $(HR_{\text{basic model}} - HR_{\text{adjusted}})/(HR_{\text{basic model}} - 1) \times 100$  (7). Key to interpretation is the degree of attenuation in the MVPA–CVD relation after adjustment, not whether the association remains significant. A statistical significance of  $P < 0.05$  was used throughout. All analyses were conducted using SPSS version 14 (IBM Corp., Armonk, NY).

## RESULTS

### Baseline characteristics

Approximately 44.0% of the sample reported undertaking some weekly MVPA. Those participants (16%) undertaking at least three sessions per week of MVPA were younger, more likely to be men, nonsmokers, not taking medication, and had a more favorable physiological risk profile (including lower adiposity, CRP, and resting heart rate and less diabetes) (Table 1).

### Physical activity and risk of death

There were a total of 446 all-cause deaths during an average of  $7.0 \pm 3.1$  yr of follow-up, of which 213 were attributed to cardiovascular causes. Participation in three or more sessions a week of MVPA was associated with lower risk of all-cause (HR = 0.52, 95% CI = 0.37–0.74) and cardiovascular death (HR = 0.61, 95% CI = 0.38–0.98), after adjustment for age, sex, smoking, and medication. To exclude the possibility of reverse causation, we removed all deaths occurring in the first 2 yr of follow-up ( $n = 99$ ), although this did not affect the results (adjusted HR for all-cause death = 0.48, 95% CI = 0.32–0.73). In the original sample of participants with available data on physical activity and basic confounders ( $n = 5145$ ), we observed similar associations of three or more sessions per week of MVPA with all-cause death (HR = 0.44, 95% CI = 0.37–0.53) and CVD death (HR = 0.43, 95% CI = 0.32–0.58) after adjustment for age, sex, smoking, and medication. Thus, these results confirm that the subsample used in the present analyses is largely representative of the overall cohort, although small differences exist in the magnitude of the effect estimates.

### Biological mediators

In multivariate models, the risk factors independently associated with cardiovascular death included total–HDL cholesterol ratio (HR per unit = 1.07, 95% CI = 1.02–1.12), natural logarithmic transformation CRP (HR per unit = 1.29, 95% CI = 1.08–1.53), and diabetes (HR = 1.92, 95% CI = 1.34–2.74). Metabolic and inflammatory risk factors explained an estimated 12.8% and 15.4% of the association between MVPA and CVD death, respectively (Table 2). Cardiovascular factors, including blood pressure and resting heart rate, did not explain any amount of the association. When we repeated the analyses excluding 365 participants taking [beta]-blockers, this did not change the results. In total, all risk factors collectively explained an estimated 25.6% of the MVPA–CVD death association.

### Behavioral mediators

To address the issue of behavioral mediators, we also conducted further analyses to examine the contribution of smoking and medication adherence. In models adjusted for only age and sex, participation in three or more sessions a week of MVPA was associated with even lower risk of cardiovascular death (HR = 0.53, 95% CI = 0.33–0.85). With the addition of smoking

to the model, the effect estimate was attenuated (HR = 0.60, 95% CI = 0.37–0.96), suggesting that smoking explained an estimated 14.9% of the MVPA–CVD death association.

## DISCUSSION

Previous evidence suggests that leisure time physical activity is important for secondary prevention in participants diagnosed with CVD, although the precise mechanisms remain incompletely understood. In the present sample of men and women with physician-diagnosed CVD from two representative health surveys, leisure time physical activity was associated with lower risk of both all-cause and cardiovascular deaths that confirms previous prospective cohort studies (2,5,8,9,12,22,25). We previously reported an inverse association between physical activity and mortality in men and women with existing CVD followed up for a shorter period in the Scottish Health Survey (8). This association was largely explained by engaging in moderate-vigorous activities such as sports and walking but not by light activities that included domestic work. This is possibly due, in part, to the lack of precise reporting of light activities.

The main finding from the present study was that, additional to the risk attributable to lower smoking prevalence, metabolic and inflammatory mechanisms explained a modest amount of the association between MVPA and CVD death. A previous work has examined the reduction in cardiac mortality attributable to changes in risk factors (total cholesterol, systolic blood pressure, and smoking) from randomized controlled trials of cardiac rehabilitation (21). Exercise-only training reduced pooled cardiac mortality by 28% (relative risk = 0.72, 95% CI = 0.55–0.95). Approximately 58% of the reduced cardiac mortality was attributable to reductions in primary CVD risk factors, especially reduced smoking prevalence. Physically active participants in this study also reported lower rates of smoking, and engaging in health behavior change might promote positive effects in several domains of lifestyle. Thus, smoking cessation might also be viewed as an intermediate mechanism in the association between physical activity and CVD risk because exercise has been used as an effective intervention in smoking cessation (20). In a prospective cohort study of predominantly male CHD patients, physical inactivity was associated with subsequent CVD events, independent of age, baseline disease severity, current smoking, and medication nonadherence. Other significant metabolic predictors of CVD events included diabetes and CRP (23). However, other factors such as blood pressure and resting heart rate did not contribute to the reduction in risk of CVD in this cohort. Franco et al. (5) evaluated risk of CVD death in males and females with preexisting CVD in the Framingham cohort. The HR for high compared with low physical activity level for CVD death was 0.67 (95% CI = 0.58–0.77). After adjustment for age, sex, smoking, and other comorbidities (including diabetes and left ventricular hypertrophy), the HR was reduced by 7% and a further 3% after adjustment for body mass index and hypertension. Our findings are similar to Mora et al. (13), who showed that an inverse association between physical activity and CVD risk was mediated in substantial part by known risk factors, particularly inflammatory/hemostatic factors and blood pressure in 27,055 apparently healthy women.

In total, our measured variables explained an estimated 25.6% of the MVPA–CVD association, which is similar to that in our previous study that contained only healthy participants (7). In both studies, inflammatory mechanisms seemed to be important, thus suggesting that some cardioprotective mechanisms of physical activity may be similar in both primary and secondary prevention. Short-term exercise training in CAD patients has been shown to reduce CRP and other proinflammatory cytokines (6). Also, an elevated CRP

level is a significant predictor of adverse cardiovascular events independently of baseline characteristics and treatments in CHD patients (17,19). We did not obtain measures of endothelial function, which is also an important prognostic indicator in CHD patients and can be modified by exercise training (24). The inclusion of this measure might have explained additional variance.

Resting heart rate is thought to be a crude indicator of cardiorespiratory fitness. Lower resting heart rate was observed in the physically active participants from the present study possibly reflecting better cardiac autonomic control. Resting heart rate was not, however, associated with cardiovascular death and did not explain the inverse association between MVPA and death. Previous studies have indicated strong associations between exercise capacity and mortality in patients referred for exercise testing (14,15). However, both an impaired capacity to increase heart rate during exercise testing (chronotropic incompetence) and a slowed rate of recovery after exercise have been associated with all-cause mortality (15) and may be considerably stronger predictors than resting heart rate. In addition, the effects of physical activity on cardiovascular health may be partly independent of cardiorespiratory fitness.

Given that lower levels of physical activity could reflect greater disease severity, we cannot discount reverse causality. We did, however, attempt to control for this potential bias by removing all deaths occurring in the first 2 yr of follow-up, which did not significantly change the nature of our findings or alter the results. The present study was based on a baseline data collection and subsequent mortality follow-up with no physical activity and other risk factor follow-up measurement. Thus, we cannot exclude the possibility that changes in physical activity behavior over time could have influenced our results. Indeed, other data suggest that men with CHD who became inactive were at the highest risk of mortality at follow-up (22). Because the Health Survey for England physical activity interview has been shown to overestimate actual activity in less active older adults with heart disease (16), the present results may have underestimated the strength of associations between activity and mortality risk. Our findings should therefore be extended and replicated by using more objective physical activity measures, such as accelerometry recordings. Lastly, the participants excluded from our study were slightly older and thus probably had poorer health and greater disease burden, which could have introduced bias into the analyses. However, the associations between physical activity and mortality in the subsample used in the present analysis were largely representative of the overall cohort.

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