Low-Dose Physical Activity Attenuates Cardiovascular Disease Mortality in Men and Women With Clustered Metabolic Risk Factors

Mark Hamer, PhD; Emmanuel Stamatakis, PhD

**Background**—Physical activity may ameliorate the health hazards of metabolic disorders but evidence is inconclusive, and estimates of the minimal threshold for protection remain unknown.

**Methods and Results**—The sample comprised 23,747 men and women (aged 54.1 ± 12.7 years [mean ± SD], 45.2% men) without a known history of cardiovascular disease at baseline who were drawn from the Health Survey for England and the Scottish Health Survey. Based on blood pressure, high-density lipoprotein cholesterol, diabetes, waist circumference, and low-grade inflammation (C-reactive protein ≥ 3 mg/L), participants were classified as metabolically healthy (zero or one metabolic abnormality) or unhealthy (≥ 2 metabolic abnormalities). Self-reported physical activity was assessed at baseline. Cox proportional hazards models were used to examine the association of clustered metabolic risk and physical activity with mortality, controlling for age, sex, smoking, socioeconomic group, cardiovascular disease medication, and self-rated health. Over 7.0 ± 3.0 years follow-up, there were 2264 all-cause and 717 cardiovascular disease deaths, respectively. A physical activity threshold of at least one to 2 sessions per week was found to provide protection against mortality. Compared with active/metabolically healthy, the active with clustered metabolic abnormalities were not at elevated risk of cardiovascular disease (hazard ratio, 0.82; 95% CI, 0.54–1.26) or all-cause mortality (hazard ratio, 1.11; 95% CI, 0.89–1.39), although their inactive counterparts were at elevated risk of cardiovascular disease (hazard ratio, 1.41; 95% CI, 1.05–1.91) and all-cause mortality (hazard ratio, 1.50; 95% CI, 1.27–1.78).

**Conclusions**—The risk of cardiovascular disease associated with poor metabolic health is substantially lower among those who are physically active. At minimum, a weekly bout of moderate to vigorous physical activity is protective in men and women with clustered metabolic abnormalities. *(Circ Cardiovasc Qual Outcomes. 2012;5:00-00.)*

**Key Words:** cardiovascular disease ■ clustered metabolic risk ■ epidemiology ■ physical activity
patients could gain benefit from incorporating a relatively low level of exercise into their treatment modalities. The aim of this study was to explore what level of physical activity is required to attenuate the risk of CVD mortality in participants with clustered metabolic abnormalities in a large nationally representative data set of men and women initially free of CVD.

**WHAT IS KNOWN**

- Physical activity can eliminate the increased risk of mortality associated with obesity.
- It is unclear if physical activity can attenuate risk in participants with a clustering of metabolic abnormalities.
- Some evidence has suggested that a low volume of activity (approximately 15 minutes a day) is associated with risk reductions.
- Given the barriers to physical activity, it would be desirable if patients could gain benefit from incorporating a relatively low level of exercise into their treatment modalities.

**WHAT THE STUDY ADDS**

- A low dose (one to 2 sessions) of moderate to vigorous physical activity is associated with reduced risk of mortality in participants with clustered metabolic risk factors.
- Physically inactive participants with metabolic risk factors were at elevated risk of CVD and all-cause mortality.
- Low-dose physical activity should be promoted in patients with metabolic risk factors.

**Methods**

**Study Design and Participants**

Participants were recruited into the Health Survey for England (HSE) and Scottish Health Survey (SHS), both representative, general population-based study sampling individuals living in households.8 HSE/SHS samples are selected using multistage-stratified probability design to give a representative sample of the target population. Stratification is based on geographical entities and not on individual characteristics: postcode sectors selected at the first stage and household addresses selected at the second stage. The overall response rate (interviewer home visit) ranged between 60% and 90% for different survey years with 33% to 41% of all eligible participants responding to the questionnaires output. The questionnaire appeared to be a valid measure of moderate to vigorous physical activity (sessions/week); intraclass correlation coefficients were 0.47 in men (P=0.03) and 0.43 in women (P=0.02).11 Additionally, these physical activity measures have demonstrated excellent convergent validity in grading a plethora of biochemical and physiological CVD risk factors by physical activities such as walking and sports.12 Weight and height were measured by the interviewers during the first home visit.

**Metabolic Risk Score**

During a second home visit, trained nurses collected information about physician-diagnosed CVD (stroke, angina, heart attack), hypertension, and diabetes mellitus (Type I and II), collected nonfasting blood samples, measured resting blood pressure, and collected information on prescribed medication. Waist circumference was taken twice to the nearest millimeter midway between the iliac crest and lower rib using a measuring tape. An average from the first 2 measurements was used although if the first and second readings differed by >3 cm, a third reading was taken. Blood samples were analyzed for C-reactive protein and high-density lipoprotein cholesterol. The analysis of C-reactive protein levels from serum was performed using the N Latex high sensitivity C-reactive protein monoinmunooassay on the Behring Nephelometer II analyzer (coefficient of variation <6%). High-density lipoprotein cholesterol was measured using cholesterol oxidase assays on an Olympus 640 analyzer. Systolic and diastolic blood pressure was measured with an Omron HEM-907 blood pressure monitor (Omron Corporation) 3 times in the sitting position after a 5-minute rest between each reading. The initial reading was discarded and an average of the second and third blood pressure recordings was used for the present analyses. Metabolic risk was based on an adaptation of previous criteria13,14 according to availability of data and defined as ≥2 metabolic abnormalities, including central obesity (waist circumference >102 cm in men and >88 cm in women), hypertension risk (clinical blood pressure >130/85 mm Hg, or hypertension diagnosis, or use of antihypertensive medication), physician-diagnosed diabetes, low-grade inflammation (C-reactive protein ≥3 mg/L), and adverse high-density lipoprotein cholesterol (<1.03 mmol/L in men and <1.30 mmol/L women).

**Mortality Follow-Up**

Classification of the primary (underlying) cause of death was based on information collected from the death certificate together with any additional information provided subsequently by the certifying physician (eg, secondary death cause). Diagnoses for primary cause of death was recorded using the International Classification of Diseases, Ninth and Tenth Revisions. Cardiovascular disease codes were 390 to 459 for International Classification of Diseases, Ninth Revision and 101 to 199 for International Classification of Diseases, Tenth Revision.

**Statistical Analyses**

For survival analysis, we used Cox proportional hazards models to compute hazard ratios (HRs) with accompanying 95% CIs. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on the various exposure variables, although no appreciable violations were noted. Months were the time scale, and for participants with no record of an event, the data were censored at February 28, 2008 (HSE) and December 31 2008 (SHS). Each model was adjusted for age, sex, smoking (never, previous,
The aim of the first analysis was to identify the threshold of physical activity required to gain protection against CVD in metabolically unhealthy participants (Table 2). Within the metabolically unhealthy participants, 24.3% reported moderate to vigorous activity at least once a week and a further 6.9% reported some activity but less than once per week. We observed a clear dose–response association showing protective effects of physical activity after adjustment for age, sex, smoking, socioeconomic group, CVD medication, self-rated health, and number of metabolic risk factors. The threshold for protective effects was observed for at least one to 2 sessions per week of activity. For example, metabolically unhealthy participants reporting one to 2 sessions of activity per week had a 49% (95% CI, 70%–15%) reduced risk of CVD death and a 33% (95% CI, 48%–13%) reduced risk of all-cause mortality after adjustment for covariates. However, there was some evidence to suggest that even less activity was associated with a reduced risk of mortality.

### Table 2. The Association Between Moderate to Vigorous Physical Activity and Mortality in Participants With Clustered Metabolic Risk Factors at Baseline (N=9100)

<table>
<thead>
<tr>
<th>MVPA Categories</th>
<th>Cases/No.</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>402/6262</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;1 session/wk</td>
<td>14/628</td>
<td>0.74 (0.43–1.27)</td>
<td>0.81 (0.47–1.38)</td>
<td>0.96 (0.56–1.65)</td>
</tr>
<tr>
<td>1–3 session/wk</td>
<td>15/1026</td>
<td>0.42 (0.25–0.71)</td>
<td>0.46 (0.27–0.78)</td>
<td>0.51 (0.30–0.85)</td>
</tr>
<tr>
<td>≥3 session/wk</td>
<td>20/1184</td>
<td>0.44 (0.28–0.69)</td>
<td>0.49 (0.31–0.77)</td>
<td>0.63 (0.40–0.99)</td>
</tr>
<tr>
<td><strong>P trend</strong></td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1126/6262</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;1 session/wk</td>
<td>38/628</td>
<td>0.63 (0.45–0.87)</td>
<td>0.69 (0.50–0.96)</td>
<td>0.78 (0.56–1.08)</td>
</tr>
<tr>
<td>1–3 session/wk</td>
<td>62/1026</td>
<td>0.56 (0.44–0.73)</td>
<td>0.63 (0.49–0.81)</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>≥3 session/wk</td>
<td>74/1184</td>
<td>0.54 (0.43–0.69)</td>
<td>0.60 (0.47–0.76)</td>
<td>0.72 (0.57–0.92)</td>
</tr>
<tr>
<td><strong>P trend</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, socioeconomic group; Model 3: adjusted for age, sex, smoking, socioeconomic group, CVD medication, self-rated health, no. of metabolic risk factors.

MVPA indicates moderate to vigorous physical activity; HR, hazard ratio; CVD, cardiovascular disease.
abnormalities was dose-dependently associated with CVD.

In the present study, we showed that the number of metabolic abnormalities clustered in participants with a clustering of metabolic abnormalities. In a previous study that examined physical activity in participants with clustered metabolic risk factors, participants were categorized above or below the median relative to the study sample, thus making it difficult to make comparison across studies. Participants with clustered metabolic risk factors who reported any light activity (activity that was considered neither moderate nor vigorous) had lower risk of CVD in the National Health and Nutrition Examination Survey (NHANES) study. In the present study, the threshold for protective effects was observed for at least one to 2 sessions per week of physical activity, although there was some evidence to suggest that even less activity (less than once per week) was protective against all-cause mortality, albeit the effect estimates did not remain significant in the fully adjusted model.

### Physical Activity, Metabolic Health, and CVD

The active/metabolically unhealthy participants were younger than their nonactive counterparts and were less likely to be current smokers, had better self-rated health, came from higher socioeconomic groups, had a lower prevalence of diabetes, and lower risk markers including blood pressure, waist, and C-reactive protein (see the online-only Data Supplement; http://circoutcomes.ahajournals.org).

There was a dose–response association between number of metabolic risk factors and CVD; compared with participants with zero or one risk factor (reference), the relative risks increased for those with 2 (HR, 1.45; 95% CI, 1.21–1.74), 3 (HR, 1.69; 95% CI, 1.39–2.08), and 4 or 5 risk factors (HR, 3.14; 95% CI, 2.48–3.98) after adjusting for age, sex, smoking, and physical activity. Compared with active/metabolically healthy, the active/metabolically unhealthy were not at elevated risk of CVD (HR, 0.82; 95% CI, 0.54–1.26) or all-cause mortality (HR, 1.11; 95% CI, 0.89–1.39), although their inactive counterparts were at elevated risk of CVD (HR, 1.41; 95% CI, 1.05–1.91) and all-cause mortality (HR, 1.50; 95% CI, 1.27–1.78; Table 3). Over 98.5% of the present sample was white, although removal of ethnic minority participants did not change any of the results.

### Discussion

Numerous studies have investigated if physical activity/high fitness can eliminate the increased risk of mortality associated with obesity. However, relatively few studies have examined whether physical activity attenuates the risk of CVD in participants with a clustering of metabolic abnormalities. In the present study we showed that the number of metabolic abnormalities was dose-dependently associated with CVD mortality after adjusting for physical activity. However, the key findings show that physically active participants with clustered metabolic risk factors are not at elevated risk of CVD mortality compared with active/healthy participants in contrast to inactive/metabolically unhealthy participants who displayed a >40% (95% CI, 5%–91%) increased risk of CVD. In addition, we observed a clear dose–response association between physical activity and CVD in participants with clustered metabolic risk factors, showing minimum protective effects at as little as 30 minutes/week moderate to vigorous physical activity.

These findings are consistent with recent data from several cohort studies that have confirmed the cardioprotective effects of physical activity in participants with clustered metabolic risk factors. However, the minimum physical activity threshold has not been well defined. In a previous study that examined physical activity in participants with clustered CVD risk factors, participants were categorized above or below the median relative to the study sample, thus making it difficult to make comparison across studies. Participants with clustered metabolic risk factors who reported any light activity (activity that was considered neither moderate nor vigorous) had lower risk of CVD in the National Health and Nutrition Examination Survey (NHANES) study. In the present study, the threshold for protective effects was observed for at least one to 2 sessions per week of physical activity, although there was some evidence to suggest that even less activity (less than once per week) was protective for all-cause mortality. Thus, particularly in participants with risk factors or patients, the threshold for protective effects of physical activity might be lower than is currently estimated. Indeed, recent evidence has suggested that a low volume of activity (3.75–7.49 metabolic equivalent-hours/week approximately 15 minutes a day) was associated with risk reductions in all-cause mortality of 10% to 20% in participants with a range of clinical conditions.
including metabolic syndrome. One of the reasons that low doses of exercise might be protective is that the dose–response gradient tends to be curvilinear with the largest health gains seen in the first 1 to 2 hours of activity a week. These findings have relevance for clinical practice because participants with risk factors may be able to gain benefit from incorporating a relatively low level of exercise into their treatment modalities.

Previous evidence has consistently shown that physical activity partly ameliorates the health hazards of obesity, for example, suggesting that physically active obese participants have lower risk of CVD than their inactive counterparts. These findings have relevance for policy and the provision of health care, because one might argue that resources should focus on promoting physical activity rather than specifically treating metabolic risk factors such as obesity. Indeed, data from training studies have shown that exercise reduces risk factors such as visceral adiposity in the absence of weight loss, which might be a key mechanism in protection from CVD among individuals with clustered risk factors. Given that physical activity was associated with CVD independently of metabolic risk factors, this suggests that “nonmetabolic”–related mechanisms are also involved such as endothelial function and cardiac performance. The nonphysically active participants without metabolic risk factors were also at elevated risk of mortality. Clinically, this might reflect an important group of people, because early intervention with exercise and diet may help prevent these participants from developing obesity and diabetes and delay the onset of overt disease.

This study uses nationally representative, longitudinal data from a well-characterized sample, which makes the findings more generalizable. Despite this, some limitations should be considered. Underlying disease may have introduced potential bias into our analyses, because participants with poorer health might have been less likely to participate in more vigorous activities. However, to address these issues, we removed any participants with existing physician-diagnosed CVD at baseline and made statistical adjustment for indicators of disease such as use of CVD medication and self-rated health, which has been shown to be a particularly robust predictor of overall health status and mortality. 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 and metabolic risk profile over time could have influenced our results. Nevertheless, if such repeated measurements were available, we might speculate that physical activity would have been more protective; thus, our results might have underestimated the true effects. Indeed, previous data have shown that in studies with a baseline-only measurement of physical activity, the association between physical activity and mortality can be diluted (underestimated) up to 60% because the activity decreases over the life course that is commonly observed in the population. Lastly, more detailed physical activity information might have provided a finer grained analysis and enabled us to more precisely define the minimum dose. We previously demonstrated an association between TV viewing and incident CVD events, which is consistent with other data that suggest sedentary behavior is a risk factor independently of physical activity. Thus, the possible interaction between sedentary behavior and metabolic risk should be considered in future research.

In summary, the present study demonstrated that a low dose of physical activity is associated with reduced risk of mortality in participants with clustered metabolic risk factors. Our results suggest that there should perhaps be a greater emphasis on promoting physical activity in primary care rather than solely targeting biological risk factors that is the current norm.

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Disclosures
None.

References


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Supplemental Material

Characteristics of the study population in relation to physical activity and metabolic health (N=23,747). Values are means ± SD unless otherwise stated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active/metabolically healthy (n=6253)</th>
<th>Non-active/metabolically healthy (n=8394)</th>
<th>Active/metabolically unhealthy (n=2210)</th>
<th>Non-active/metabolically unhealthy (6890)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.4±10.9</td>
<td>54.5±13.3</td>
<td>54.1±11.8a</td>
<td>60.0±12.9</td>
</tr>
<tr>
<td>Men (%)</td>
<td>46.7</td>
<td>45.6</td>
<td>44.1</td>
<td>43.8</td>
</tr>
<tr>
<td>Low Socioeconomic group (%)</td>
<td>13.3</td>
<td>21.5</td>
<td>18.1a</td>
<td>25.1</td>
</tr>
<tr>
<td>Poor self-rated health (%)</td>
<td>1.1</td>
<td>5.9</td>
<td>3.3b</td>
<td>12.6</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>18.6</td>
<td>29.6</td>
<td>19.1b</td>
<td>25.7</td>
</tr>
<tr>
<td>CVD medication (%)</td>
<td>5.6</td>
<td>10.4</td>
<td>27.6a</td>
<td>39.2</td>
</tr>
<tr>
<td>Physical activity (Average sessions per week)</td>
<td>4.6±3.4</td>
<td>0.1±0.1</td>
<td>3.9±2.9a</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.62±0.4</td>
<td>1.58±0.4</td>
<td>1.33±0.4c</td>
<td>1.32±0.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3±3.2</td>
<td>25.5±3.6</td>
<td>30.3±4.8c</td>
<td>30.4±5.0</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>85.2±10.4</td>
<td>86.1±10.8</td>
<td>98.6±11.5a</td>
<td>100.1±12.4</td>
</tr>
<tr>
<td>Central obesity (%)</td>
<td>9.8</td>
<td>12.0</td>
<td>71.4a</td>
<td>71.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0.4</td>
<td>0.5</td>
<td>4.3a</td>
<td>7.7</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127.3±15.9</td>
<td>131.3±18.5</td>
<td>140.1±19.8a</td>
<td>143.5±20.9</td>
</tr>
<tr>
<td>Hypertension risk (%)</td>
<td>16.8</td>
<td>19.7</td>
<td>67.6c</td>
<td>68.9</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>1.68±3.5</td>
<td>2.31±5.3</td>
<td>5.07±6.4a</td>
<td>6.98±8.9</td>
</tr>
<tr>
<td>Inflammation (CRP≥3mg/l) (%)</td>
<td>10.2</td>
<td>13.6</td>
<td>58.7a</td>
<td>69.6</td>
</tr>
<tr>
<td>No. metabolic risk factors</td>
<td>0.4±0.5</td>
<td>0.5±0.5</td>
<td>2.4±0.6a</td>
<td>2.6±0.7</td>
</tr>
</tbody>
</table>

a significantly different (p<0.05) from all other groups; b significantly different from non-active groups; c significantly different from metabolically healthy group