Original Contribution

Physical Activity and Mortality: Is the Association Explained by Genetic Selection?

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Public health recommendations promote physical activity to improve health and longevity. Recent data suggest that the association between physical activity and mortality may be due to genetic selection. Using data on twins, the authors investigated whether genetic selection explains the association between physical activity and mortality. Data were based on a postal questionnaire answered by 13,109 Swedish twin pairs in 1972. The national Cause of Death Register was used for information about all-cause mortality (n = 1,800) and cardiovascular disease mortality (n = 638) during 1975–2004. The risk of death was reduced by 34% for men (relative risk = 0.64, 95% confidence interval: 0.50, 0.83) and by 25% for women (relative risk = 0.75, 95% confidence interval: 0.50, 1.14) reporting high physical activity levels. Within-pair comparisons of monozygotic twins showed that, compared with their less active co-twin, the more active twin had a 20% (odds ratio = 0.80, 95% confidence interval: 0.65, 0.99) reduced risk of all-cause mortality and a 32% (odds ratio = 0.68, 95% confidence interval: 0.49, 0.95) reduced risk of cardiovascular disease mortality. Results indicate that physical activity is associated with a reduced risk of mortality not due to genetic selection. This finding supports a causal link between physical activity and mortality.

mortality; motor activity; questionnaires; selection (genetics); Sweden; twins

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.

Editor's note: An invited commentary on this article is published on page 260.

Public health recommendations promote exercise to improve health and longevity. Such recommendations originate primarily from observational studies showing that physical activity is associated with reduced morbidity (1) and mortality (2–4), especially from cardiovascular disease (CVD) (5). Results from a recent study based on the Finnish Twin Cohort suggest that the association between physical activity and mortality may be due to genetic selection (6). However, because the study was based on a small number of physical-activity-discordant twin pairs, these results were uncertain. Thus, replications of this study are needed.

The idea of a genetic explanation behind the association is not far-fetched. Studies have indicated that there is a genetic component to physical activity on the order of 29–62 percent (7–11). In addition, a large number of twin studies have shown that susceptibility to disease and longevity is heritable (12–15). If the same genes that contribute to an active
lifestyle also increase longevity, a spurious association between physical activity and mortality may arise in observational studies.

In this study, we used data from the Swedish Twin Registry to investigate the genetic influence on the association of physical activity with all-cause mortality and CVD mortality.

MATERIALS AND METHODS

Participants

This study was based on the “middle cohort” of the Swedish Twin Registry. This cohort includes all twins born from 1926 through 1958 who were alive and living in Sweden in 1970 (16). In 1972, all same-sex pairs received a questionnaire including items on lifestyle factors such as physical activity. Responses that enabled zygosity to be determined were received from 16,120 pairs. The response rate was 88 percent. The analyses in this paper are based on data from the 13,109 twin pairs for whom information on physical activity, smoking, and zygosity was complete. The Swedish Twin Registry has been approved by the Data Inspection and the Ethical Committee at Karolinska Institutet.

Zygosity

Zygosity of twins (monozygotic, dizygotic, unclassified) was classified on the basis of the following question: Were you as children as alike as two peas in a pod? When both twins answered affirmatively, they were defined as monozygotic; when both answered no, they were defined as dizygotic. This method has been proven to correctly classify more than 95 percent of twins (17).

Physical activity

Information on physical activity was collected by using an item in the 1972 questionnaire on average physical activity during leisure time in the past year, with seven response options: 1) “almost never,” 2) “hardly ever,” 3) “very little,” 4) “not much,” 5) “quite much,” 6) “a lot,” and 7) “very much.” For the analyses, we combined these categories into three groups and defined low physical activity as exercise “almost never” to “hardly ever,” moderate physical activity as “very little” to “quite much,” and high physical activity as “a lot” to “very much.”

Other covariates

The 1972 questionnaire included items on height and weight. Body mass index was calculated as weight in kilograms divided by the square of height in meters. On the basis of information about current and previous smoking, subjects were classified as never, former, or current smokers. Alcohol consumption was assessed by separate questions on the amount of beer, wine, and spirits consumed during a month. This information was used to calculate alcohol consumption in grams per month. For the analyses, this variable was divided into six categories. Subjects were also asked whether they had any long-term or serious illness.

Mortality

Information on deaths was obtained by linkage to the national Cause of Death Register using the personal identification number assigned to every Swedish citizen. This register includes information on all deaths in Sweden, with cause of death classified according to the International Classification of Diseases. All deaths during 1973–2004 were identified, including deaths due to CVD as the primary or secondary cause of death (International Classification of Diseases, Eighth Revision and Ninth Revision, codes 390–459 and, later, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, codes I00–I99). Our classification did not include congenital heart disease as CVD.

Data analysis

Person-years of follow-up were accumulated from age at start of the study (January 1, 1975). Follow-up was lagged by 2 years to exclude subjects who died shortly after filling out the questionnaire and hence may have been too ill to exercise at baseline. Follow-up was terminated at age at death or at age at the end of follow-up (June 30, 2004), whichever occurred first. We used age as the underlying time scale. To analyze the association between physical activity and all-cause and CVD mortality, we calculated relative risk estimates together with 95 percent confidence intervals by using Cox proportional hazards models (SURVIVAL 2.16 package with Coxph in R 2.0 (18)). A frailty component was included in the Cox model to handle within-pair dependences. Physical activity was analyzed in three categories, with the lowest group as the reference. To adjust for confounding, we included smoking in the Cox model. Additional adjustment for alcohol consumption, body mass index, and serious or long-term illness did not affect the relative risk estimates, and these variables were therefore not included in the final model.

To investigate the association between physical activity and mortality, taking hereditary factors into account, we used multivariate logistic regression. We made these analyses conditional on pair membership and estimated odds ratios with 95 percent confidence intervals in physical-activity-discordant twin pairs. This procedure was performed separately for monozygotic and dizygotic twins. In the first analysis, pairs were considered discordant for physical activity if their answers regarding the seven original response options were not the same. In the second analysis, we used the combined physical activity categories—low, moderate, and high—corresponding to the individual-based analyses and considered a pair discordant if the twin and cotwin were in different groups.

RESULTS

The same-sex twin pairs included 5,240 who were monozygotic (2,406 male and 2,834 female) and 7,869 who were dizygotic (3,750 male and 4,119 female) (table 1). The age range was 14–46 years at baseline, with a mean age of 28.8 years. During follow-up, including 690,355 person-years,
1,800 deaths occurred (1,014 in men, 786 in women); CVD was a contributing cause for 683 of them (434 in men and 249 in women).

The relative risk of all-cause mortality was reduced by 36 percent (95 percent confidence interval (CI): 17 percent, 50 percent) for men reporting high physical activity levels compared with men reporting low physical activity levels. For women, the corresponding risk reduction was 25 percent (95 percent CI: 14 percent, 50 percent) (table 2). The association was more pronounced for death from cardiovascular-related causes, indicating a 45 percent (95 percent CI: 15 percent, 64 percent) reduced risk among very active men and a 66 percent (95 percent CI: 5 percent, 88 percent) reduced risk among very active women.

Analyses of physical-activity-discordant, monozygotic twin pairs indicated that the twin with higher physical activity had a 20 percent (95 percent CI: 1 percent, 35 percent) lower mortality risk (table 3) when compared with the less active co-twin. For cardiovascular mortality, a 32 percent (95 percent CI: 5 percent, 51 percent) risk reduction was seen in the more active twin. The association was less pronounced among dizygotic twins (table 2). When these analyses were stratified by sex, the odds ratios of all-cause mortality were 0.82 (95 percent CI: 0.62, 1.08) for male monozygotic twins and 0.79 (95 percent CI: 0.58, 1.07) for female monozygotic twins.

The results were similar when we used the same physical activity categories as in the individual-based analyses, and we regarded the pair as discordant if their answers were not the same for the three physical activity categories, that is, low, moderate, and high (not shown in the tables). For monozygotic twins, these analyses indicated a relative risk of 0.84 (95 percent CI: 0.64, 1.11) for all-cause mortality and of 0.70 (95 percent CI: 0.45, 1.10) for CVD deaths.

**DISCUSSION**

This study confirms many previous findings indicating that physical activity is associated with a reduced risk of all-cause mortality (2–4), particularly regarding death from cardiovascular causes (5). However, the main finding of this study was that the association between physical activity and mortality was found within monozygotic twin pairs, which supports a causal link between physical activity and mortality. We thus did not find support for a genetic explanation.

**TABLE 1. Baseline characteristics of monozygotic and dizygotic male and female twins, Swedish Twin Registry, 1972**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monozygotic</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>No. of twins</td>
<td>4,812</td>
<td>7,500</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>30.6 (9.1)*</td>
<td>30.5 (9.2)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
<td>22.4 (2.8)</td>
<td>22.5 (2.8)</td>
</tr>
<tr>
<td>Overweight (body mass index ≥25) (%)</td>
<td>16.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Long-term or serious illness (%)</td>
<td>15.1</td>
<td>14.8</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>46.8</td>
<td>49.5</td>
</tr>
<tr>
<td>High physical activity level (%)</td>
<td>17.7</td>
<td>16.2</td>
</tr>
</tbody>
</table>

* Values in parentheses, standard deviation.


<table>
<thead>
<tr>
<th>Sex and physical activity level</th>
<th>No. of person-years</th>
<th>All-cause mortality</th>
<th>Cardiovascular disease mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Hazard ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Men Low</td>
<td>64,499</td>
<td>263</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>202,864</td>
<td>661</td>
<td>0.84</td>
</tr>
<tr>
<td>High</td>
<td>54,895</td>
<td>90</td>
<td>0.64</td>
</tr>
<tr>
<td>Women Low</td>
<td>90,897</td>
<td>241</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>258,012</td>
<td>518</td>
<td>0.82</td>
</tr>
<tr>
<td>High</td>
<td>19,188</td>
<td>27</td>
<td>0.75</td>
</tr>
</tbody>
</table>
behind the association of physical activity with mortality, as suggested by previous findings (6).

Current knowledge on the association between physical activity and mortality originates primarily from observational studies (2–4), meaning that competing explanations besides a causal link need careful consideration. Because monozygotic twins are genetically identical, the twin design is an invaluable tool to control for genetic confounding. If monozygotic twins discordant with regard to a specific risk factor are investigated and disease is equally frequent in both twins, this finding indicates that the association between exposure and disease seen in individual-based analyses is due to genetic selection. This was the situation in the Finnish Twin Cohort, where no association was found between physical activity and mortality in monozygotic twins (6). In contrast, the present study indicated a 20 percent reduced risk of all-cause mortality and a 30 percent reduced risk of CVD-related mortality in active monozygotic twins compared with their less active co-twins. Our results thus support a causal link between physical activity and mortality. The discrepancy between the present results and previous results from the Finnish Twin registry may have several explanations. The Finnish study is based on only 68 twin pairs discordant with regard to all-cause mortality and CVD mortality for monozygotic twins. On the contrary, the most likely consequence of our crude information on physical activity would be underestimation of the true association. It should also be noted that in spite of the simplicity of our information on physical activity. The analyses were based on a single question about average physical activity during leisure time. Still, the crudeness of our information is not likely to have resulted in a spurious association between physical activity and mortality for monozygotic twins. The explanation for this association. Hence, this study supports the finding that physical activity is associated with a reduced risk of all-cause and CVD mortality. The association between physical activity and mortality was seen within monozygotic twin pairs. This finding provides strong support against genetic selection as the explanation for this association. Hence, this study supports a causal link between physical activity and mortality, suggesting that life expectancy can be prolonged with physical activity.

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Conflict of interest: none declared.
REFERENCES