Physical Activity and 23-Year Incidence of Coronary Heart Disease Morbidity and Mortality Among Middle-aged Men

The Honolulu Heart Program

Beatriz L. Rodriguez, MD, PhD; J. David Curb, MD; Cecil M. Burchfiel, PhD; Robert D. Abbott, PhD; Helen Petrovitch, MD; Kamal Masaki, MD; Darryl Chiu, MS

Background The purpose of the study was to examine the association between physical activity and 23-year incidence of coronary heart disease morbidity and mortality. This cohort study continues to follow 8006 Japanese-American men who were 45 to 68 years of age and living on Oahu, Hawaii, in 1965, for the development of coronary heart disease morbidity and mortality.

Methods and Results The Framingham physical activity index was calculated by summing the product of average hours spent at each activity level and a weighting factor based on oxygen consumption. Study subjects were divided into tertiles of physical activity index at baseline. Relative risks and 95% confidence intervals (CI) for incidence of coronary heart disease morbidity and mortality were obtained using the Cox model. After age adjustment and using the lowest physical activity index tertile as a reference group, the relative risk for coronary heart disease incidence for the highest tertile of physical activity was 0.83 (CI, 0.70 to 0.99). After adjusting for age, hypertension, smoking, alcohol intake, diabetes, cholesterol, and body mass index, the relative risk was 0.95 and CI included 1 (CI, 0.80 to 1.14). For coronary heart disease mortality, the age-adjusted relative risk was 0.74 (CI, 0.56 to 0.97) and 0.85 (CI, 0.65 to 1.13) after risk factor adjustment.

Conclusions The results suggest that the impact of physical activity index on coronary heart disease is mediated through its effects on hypertension, diabetes, cholesterol, and body mass index. These findings support the hypothesis that physical activity is inversely associated with coronary heart disease morbidity and mortality and suggest that physical activity interventions in middle-aged men, by improving cardiovascular risk factor levels, may have significant public health implications in the prevention of coronary heart disease. (Circulation. 1994;89:2540-2544.)

Key Words • exercise • coronary heart disease • Japanese-Americans • middle age

The identification of factors that may prevent the development of coronary heart disease is clearly important because this condition continues to be the leading cause of death in Western industrialized countries. The inverse relation between physical activity and coronary heart disease remains controversial. Recently, a meta-analysis of 27 studies that examined this relation presented convincing evidence that physical activity has a protective effect against coronary heart disease. However, whether the association between physical activity and coronary heart disease is independent of other cardiovascular risk factors is debatable.

The Honolulu Heart Program provides the opportunity to investigate the association between physical activity and incidence of coronary heart disease morbidity and mortality among men aged 45 to 64 years during a follow-up period of up to 23 years in a cohort of 8006 men of Japanese ancestry. A previous publication from the Honolulu Heart Program reported a protective effect of physical activity on coronary heart disease incidence during 12 years of follow-up. This investigation extends the follow-up period to 23 years and includes coronary heart disease mortality as an outcome in addition to morbidity. It also provides results adjusted for multiple risk factors simultaneously, as opposed to adjustment for individual risk factors separately. Few studies have been able to examine these relations among middle-aged men with such a long follow-up period.

Methods

Study Population

The Honolulu Heart Program began in Oahu, Hawaii, in 1965 to 1968, following 8006 men of Japanese ancestry, then aged 45 to 68 years, for the development of coronary heart disease and stroke. Details of the selection process for this cohort have been published previously. Prevalent cases of coronary heart disease, stroke, and cancer were excluded from these analyses. Also, participants aged 65 years or older were eliminated because retirement may have a significant impact on physical activity habits. A total of 7074 men were included in the analyses.

Data Collection

Baseline Examination

During the first examination of this cohort in 1965, data on cardiovascular risk factors were collected using a standard
protocol. Data collected included anthropometric measurements, blood pressure measurements, ECG, serum cholesterol levels, behavioral characteristics such as smoking, alcohol consumption, and physical activity, and medical history, among other variables. An examination by a physician also was conducted. The information on physical activity obtained at the baseline examination included the average number of hours spent per day in various levels of activity including no activity such as sleeping or lying down, sedentary activity such as sitting or standing, slight activity such as walking on level ground, moderate activity such as gardening or light carpentry, and heavy activity such as shoveling or digging. These data were collected once as part of the first examination. Similar questionnaires have been used by the Framingham* and Puerto Rico-10 heart studies.

Surveillance Methods

A surveillance system was established at the beginning of the study and continues to identify cases of coronary heart disease and stroke, based on selected discharge diagnoses at the major medical facilities on the island of Oahu. The ascertainment of death is primarily from obituaries in island newspapers, supplemented with listings of death certificates filed with the State Department of Health. The medical records are then requested and reviewed by a panel of Honolulu Heart Program physicians to identify incident cases of heart disease and stroke as well as to determine the cause of death, based on standardized criteria.11,12 Incident cases of coronary heart disease include fatal and nonfatal events as well as sudden deaths within 1 hour among asymptomatic or apparently healthy subjects. The out-migration rate from Oahu for our study participants has been less than 1 in 1000 per year.

Data Analysis

To calculate a summary measure of physical activity, a weighting factor based on the approximate oxygen consumption needed for each level of effort was multiplied by the number of hours spent at each level of activity. The resulting products of all levels of activity then were added to obtain a physical activity index.5

The mean number of hours spent in each level of physical activity was calculated for the population in the study. Subjects then were divided into tertiles based on their physical activity index level. Age-adjusted mean values (or percentages) for selected risk factors and age-adjusted incidence rates per 1000 person-years for coronary heart disease morbidity and mortality were calculated by tertile of physical activity. To examine the effect of physical activity on coronary heart disease morbidity and mortality and the potential mediating effects of other risk factors on such a relation, Cox regression models were used.13 Estimates of relative risk were obtained using the subjects in the lowest tertile of physical activity as the reference group. Analyses were repeated excluding deaths that occurred within the first 2 years of follow-up. Analyses also were conducted using the number of hours spent in various levels of activity individually instead of using the composite physical activity index. To address the possibility that the effect of physical activity on the risk of coronary heart disease might be altered as follow-up becomes further removed from when physical activity was first assessed, the effect of physical activity was allowed to change with time in the Cox regression model.

Results

Table 1 shows the mean number of hours per day spent at each level of physical activity among participants in the study. On average, subjects spent 7.3 hours per day inactive, 7.3 hours performing sedentary activities, 6.1 hours in slight activities, 3.1 hours in moderate activities, and 0.2 hours conducting heavy activities.

The study population was divided into tertiles based on the physical activity index. Ninety percent of the men in the lower tertile spent 15 hours per day inactive or sedentary and 0 hours in moderate or heavy activities. In contrast, 90% of the men in the upper tertile spent 10 hours of the day inactive or sedentary and 5 hours conducting moderate or heavy activities. Ninety percent of the men in the middle tertile spent 11 hours per day inactive or sedentary and 1 hour in moderate or heavy activities.

Among men in the most active group, less than 1% reported mostly sitting at work and 40% reported mostly sitting at home. In contrast, 54% of the inactive men reported mostly sitting at work and 72% reported mostly sitting at home.

Age-adjusted mean levels (or percentages) of selected cardiovascular risk factors are shown by tertile of physical activity index in Table 2. By design, the physical activity index increased with increasing tertile of physical activity. Smoking and alcohol consumption did not vary significantly across physical activity index tertiles. Body mass index, serum cholesterol, and rates of hypertension and diabetes decreased significantly with increasing levels of physical activity.

During the 23 years of follow-up, 789 incident cases of coronary heart disease were identified (fatal and nonfatal events). A significantly lower age-adjusted incidence rate was observed among men in the highest tertile of physical activity index, 5.2 per 1000 person-years compared with 6.3 and 6.2 per 1000 person-years in the middle and lowest tertiles, respectively. No protective effect was observed at moderate levels of physical activity. The test for trend was of borderline significance (P = .06) (Fig 1).

During the follow-up period, 340 fatal coronary heart disease events occurred. Age-adjusted mortality rates for coronary heart disease were also lowest among men in the highest tertile of physical activity, 1.9 per 1000 person-years compared with 2.9 and 2.6 per 1000 among the middle and lowest physical activity index tertiles (Fig 2). Again, no protective effect was evident for men reporting moderate levels of activity. The test for trend was also of borderline significance (P = .05).

Cox regression models were used to study the relation of physical activity index and other risk factors to the risk of total coronary heart disease incidence (Table 3). No significant association was observed between intermediate levels of physical activity at baseline and 23-year incidence of coronary heart disease. Participants in the highest physical activity index tertile at baseline showed a 17% reduction in 23-year coronary heart disease incidence (relative risk, 0.83; 95% confidence interval, 0.70 to 0.99) after adjusting for age. This
Inverse relation between physical activity and risk of coronary heart disease was also independent of smoking and alcohol consumption. However, when each of the variables hypertension, cholesterol, body mass index, and diabetes were included separately in the model with age, the 95% confidence intervals for the relative risk for total coronary heart disease incidence among the most active men included 1 in the various models. In a separate regression that included all risk factors, the relative risk of physical activity for total coronary heart disease incidence was 0.95 (95% confidence interval, 0.80 to 1.14).

Similar analyses were conducted for coronary heart disease mortality (Table 4). The findings observed were consistent but of a larger magnitude compared with total coronary heart disease incidence. Participants in the highest tertile of physical activity index showed a 26% reduction in 23-year coronary heart disease mortality (relative risk, 0.74; 95% confidence interval, 0.56 to 0.97) after adjusting for age. In a Cox model that included all risk factors, the relative risk of coronary heart disease death for the most physically active tertile was 0.85 (95% confidence interval, 0.65 to 1.13).

Analyses were repeated excluding deaths that occurred within the first 2 years of follow-up, and results were unchanged. Analyses also were repeated using the number of hours spent inactive or sedentary as well as in moderate and heavy activities separately instead of using the composite index. No additional insights were available from these procedures. Although associations tended to be weaker, the risk of coronary heart disease increased with more hours spent inactive or sedentary and decreased with more hours spent in moderate or heavy activities. In general, the physical activity index was a better predictor of the risk of coronary heart disease, presumably because of the ability of the composite physical activity index to incorporate all information that comprises the overall metabolic output in a 24-hour period compared with the individual components of activity that define the physical activity index.

To test for a potential decline in the strength of the association between physical activity and coronary heart disease incidence as the number of years of follow-up increases, the effect of physical activity on the risk of coronary heart disease was allowed to change with time from when the physical activity index was first measured (1965 to 1968). Although the association of physical activity with coronary heart disease seemed to decline with increasing number of years into follow-up, the decline was not statistically significant.

**Discussion**

The findings of this long-term epidemiologic study suggest that among men of middle age, leading a physically active lifestyle was associated with a significant reduction in the risk of coronary heart disease.

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**Table 2.** Age-Adjusted Mean Risk Factor Levels by Tertile of Physical Activity Index Among Men Aged 45 to 64 Years at Exam 1

<table>
<thead>
<tr>
<th>Physical Activity Index Tertile</th>
<th>Low (SD)</th>
<th>Medium (SD)</th>
<th>High (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity index</td>
<td>29 (1.1)</td>
<td>32 (1.2)*</td>
<td>38 (3.8)*</td>
</tr>
<tr>
<td>Smoking, pack/yr</td>
<td>17 (24.6)</td>
<td>17 (24.2)</td>
<td>18 (22.9)</td>
</tr>
<tr>
<td>Alcohol, oz/mo</td>
<td>14 (24.4)</td>
<td>14 (24.5)</td>
<td>15 (25.0)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.2 (3.1)</td>
<td>24.0 (3.2)*</td>
<td>23.4 (3.0)*</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>220 (38.7)</td>
<td>218 (37.5)</td>
<td>217 (38.0)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39% (0.5)</td>
<td>36% (0.5)*</td>
<td>33% (0.5)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15% (0.4)</td>
<td>13% (0.3)*</td>
<td>11% (0.3)*</td>
</tr>
</tbody>
</table>

Prevalent cases of coronary heart disease, cerebrovascular disease, and cancer were excluded.

*P < .05, lowest tertile of physical activity index as reference.
morbidities and mortality. This effect appears to be mediated through the effect of physical activity on other cardiovascular risk factors such as hypertension, body mass index, serum cholesterol, and diabetes. These findings are consistent with other studies that have shown that physical activity may offer protection against coronary heart disease.4,5,7,9,10,13-32 This study also supports the hypothesis, at least cross-sectionally, that physical activity is associated with a favorable profile of cardiovascular disease risk factors27,33 and that this association is related to the prediction of coronary heart disease morbidity and mortality.

Although these results, based on 23 years of follow-up, show slightly weaker associations between physical activity and coronary heart disease incidence compared with those reported by Donahue et al.,5 the latter using only the first 12 years of follow-up, the differences are not statistically significant. The present findings can only suggest the potential for a decline in the strength of association between physical activity and coronary heart disease with increasing number of years of follow-up after physical activity is assessed and that long-term follow-up studies may warrant more frequent updating of physical activity information to better characterize or strengthen the associations that are reported here.

This study, like other observational investigations on this matter, has various potential sources of bias.27,29 The measurement of physical activity used in this investigation is a self-reported measure, which does not obtain very detailed descriptions of activity, as do some more recently developed instruments. Breaking down the physical activity index into its individual components failed to identify a specific component of the physical activity index that may have been responsible for the overall association that was found between the physical activity index and coronary heart disease. Also, changes in physical activity habits may have occurred during the follow-up period. Thus, we cannot rule out the possibility of systematic misclassification among the three physical activity groups. This type of misclassification could potentially increase or decrease the magnitude of the association observed between physical activity and coronary heart disease.

In this investigation, a dose-response effect for coronary heart disease morbidity and mortality incidence rates across tertiles of physical activity index was not evident. Men in the middle tertile even showed slightly higher coronary heart disease morbidity and mortality rates compared with the most inactive group. The

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**TABLE 3. Relative Risks and 95% Confidence Intervals for Total Coronary Heart Disease Incidence by Level of Physical Activity Index Among Men Aged 45 to 64 Years at Exam 1 During a 23-Year Follow-up Period Adjusting for Selected Variables**

<table>
<thead>
<tr>
<th>Variables in the Model</th>
<th>Middle Tertile RR (95% CI)</th>
<th>Highest Tertile RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.86-1.19)</td>
<td>0.83 (0.70-0.99)*</td>
</tr>
<tr>
<td>Age, smoking</td>
<td>1.00 (0.85-1.18)</td>
<td>0.82 (0.69-0.98)*</td>
</tr>
<tr>
<td>Age, alcohol</td>
<td>1.02 (0.86-1.20)</td>
<td>0.84 (0.70-0.99)*</td>
</tr>
<tr>
<td>Age, hypertension</td>
<td>1.04 (0.88-1.22)</td>
<td>0.87 (0.73-1.03)</td>
</tr>
<tr>
<td>Age, cholesterol</td>
<td>1.03 (0.87-1.22)</td>
<td>0.86 (0.72-1.02)</td>
</tr>
<tr>
<td>Age, body mass index</td>
<td>1.04 (0.88-1.23)</td>
<td>0.89 (0.75-1.06)</td>
</tr>
<tr>
<td>Age, diabetes</td>
<td>1.04 (0.88-1.23)</td>
<td>0.87 (0.73-1.03)</td>
</tr>
<tr>
<td>All variables above</td>
<td>1.07 (0.90-1.26)</td>
<td>0.95 (0.80-1.14)</td>
</tr>
</tbody>
</table>

Prevalent cases of coronary heart disease, cerebrovascular disease, and cancer were excluded. Reference group was the lowest physical activity index tertile.

*95% confidence interval (CI) for the relative risk (RR) excludes 1.

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**TABLE 4. Relative Risks and 95% Confidence Intervals for Coronary Heart Disease Mortality by Level of Physical Activity Index Among Men Aged 45 to 64 Years at Exam 1 During a 23-Year Follow-up Period Adjusting for Selected Variables**

<table>
<thead>
<tr>
<th>Variables in the Model</th>
<th>Middle Tertile RR (95% CI)</th>
<th>Highest Tertile RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.12 (0.88-1.44)</td>
<td>0.74 (0.56-0.97)*</td>
</tr>
<tr>
<td>Age, smoking</td>
<td>1.12 (0.88-1.44)</td>
<td>0.72 (0.54-0.95)*</td>
</tr>
<tr>
<td>Age, alcohol</td>
<td>1.13 (0.88-1.45)</td>
<td>0.74 (0.56-0.98)*</td>
</tr>
<tr>
<td>Age, hypertension</td>
<td>1.15 (0.90-1.48)</td>
<td>0.77 (0.59-1.02)</td>
</tr>
<tr>
<td>Age, cholesterol</td>
<td>1.14 (0.89-1.47)</td>
<td>0.76 (0.58-1.00)</td>
</tr>
<tr>
<td>Age, body mass index</td>
<td>1.15 (0.90-1.48)</td>
<td>0.79 (0.60-1.04)</td>
</tr>
<tr>
<td>Age, diabetes</td>
<td>1.17 (0.91-1.50)</td>
<td>0.79 (0.60-1.04)</td>
</tr>
<tr>
<td>All variables above</td>
<td>1.19 (0.93-1.53)</td>
<td>0.85 (0.65-1.13)</td>
</tr>
</tbody>
</table>

Prevalent cases of coronary heart disease, cerebrovascular disease, and cancer were excluded. Reference group was the lowest physical activity index tertile.

*95% confidence interval (CI) for the relative risk (RR) excludes 1.
patterns of activity of men in the middle tertile, however, are more like those of men in the lower physical activity tertile than the activity patterns of men in the most active group. For example, 90% of the men in the lower and middle tertile of physical activity spent 0 and 1 hours, respectively, conducting moderate or heavy activities, compared with 5 hours for the top tertile. This may explain why only the most active group showed reduced incidence rates of coronary heart disease morbidity and mortality.

The major potential source of bias in this type of investigation could be due to the possibility that subjects who had low levels of physical activity at entry were already sick, and illness was the cause rather than the result of lack of physical activity. Efforts to reduce this potential source of bias were made by eliminating all prevalent cases of heart disease, stroke, and cancer from these analyses. Analyses were also repeated after excluding deaths occurring during the first 2 years of follow-up, and results did not change. It is also possible that subjects who exercise may have adopted other healthy habits besides physical activity, leading to confounding of the results. However, the physical activity measure used in this study reflects the overall level of activity of the subjects throughout the day rather than only whether participants engage in sports, a behavior potentially linked to other healthy habits. No doubt, a randomized, controlled clinical trial of physical activity would be the optimal way to assess the potential benefits of physical activity on coronary heart disease incidence and mortality and would allow the establishment of the temporal relation between cause and effect. Unfortunately, this type of investigation may not be feasible because of difficulty with long-term compliance and the resources that a study of this nature would require. Despite the problems of observational studies, the evidence suggesting that lack of physical activity is a potentially modifiable risk factor for coronary heart disease morbidity and mortality continues to accumulate.4,5,7,9,10,15-32 These findings suggest that physical activity interventions during middle age, by improving cardiovascular risk factor levels, may have significant public health implications for the prevention of coronary heart disease.

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