Objective: To examine the role of nonfasting serum insulin level and components of the insulin resistance syndrome in the relationship between physical activity and the incidence of coronary heart disease and type 2 diabetes.

Methods: Prospective study of 5159 men aged 40 to 59 years with no history of coronary heart disease, type 2 diabetes, or stroke drawn from general practices in 18 British towns. During an average follow-up period of 16.8 years, there were 616 cases of major coronary heart disease events (fatal and nonfatal) and 196 incident cases of type 2 diabetes.

Results: After adjustment for potential confounders (lifestyle characteristics and preexisting disease), physical activity was inversely related to coronary heart disease rates, with the lowest rates in the men undertaking moderate physical activity and with no further benefit thereafter. For type 2 diabetes, risk decreased progressively with increasing levels of physical activity. Physical activity was associated with serum insulin level and with factors associated with insulin, ie, heart rate, hyperuricemia, diastolic blood pressure, and high-density lipoprotein cholesterol level, and with γ-glutamyltransferase level, a possible marker of hepatic insulin resistance. Adjustment for insulin and associated factors made little difference to the relationship between physical activity and risk of coronary heart disease. By contrast, these factors together with γ-glutamyltransferase level appear to explain a large proportion of the reduction in risk of type 2 diabetes associated with physical activity.

Conclusions: The relationship between physical activity and type 2 diabetes appears to be mediated by serum true insulin level and components of the insulin resistance syndrome. However, these factors do not appear to explain the inverse relationship between physical activity and coronary heart disease.

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IT IS WELL ESTABLISHED that regular physical activity in leisure time is independently associated with a reduction in the risk of major coronary heart disease (CHD) events and type 2 diabetes. Many mechanisms have been invoked to explain the relationships, including effects on insulin sensitivity, lipoprotein metabolism, blood pressure, fibrinolytic activity, and hemostatic function. Most studies have shown the associations between physical activity and CHD and type 2 diabetes to be independent of cardiovascular risk factors, including blood pressure, blood lipid levels (total cholesterol and high-density lipoprotein [HDL] cholesterol), and blood glucose level.

Insulin resistance and hyperinsulinemia play an important role in the etiology of type 2 diabetes and have been linked with increased risk of CHD. Hyperinsulinemia is frequently associated with an atherogenic profile, and it has been proposed that insulin resistance is a basic component of a metabolic syndrome that involves hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension. There is good evidence that regular exercise enhances insulin sensitivity and reduces insulin resistance and hyperinsulinemia. It has been postulated that the beneficial influence of physical activity on type 2 diabetes may act through a direct effect on increased sensitivity to insulin and that insulin may be a mediating factor in the physical activity–CHD relationship. However, few prospective studies have investigated the role of insulin as a mediating factor in the relationship between physical activity and CHD or type 2 diabetes.

Previous reports on this cohort of men have shown physical activity to be associated with decreased risk of both CHD and type 2 diabetes, and these associations were independent of lifestyle characteristics, blood pressure, and blood lipid levels.
SUBJECTS AND METHODS

The British Regional Heart Study is a large prospective study of cardiovascular disease comprising 7735 men aged 40 to 59 years selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported.20 Research nurses administered a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. The men were asked to recall a physician’s diagnosis of angina, myocardial infarction (heart attack or coronary thrombosis), stroke, diabetes, and several other disorders listed on the questionnaire.

Details of the classification of smoking habits, alcohol intake, social class, and physical activity have been reported.19 The men were classified according to their current smoking status: those who had never smoked, ex-cigarette smokers, and current smokers at 4 levels (1-19, 20, 21-39, and ≥40 cigarettes per day). Heavy drinking was defined as drinking more than 6 alcoholic drinks daily or most days in the week (1 drink equals 8-10 g of alcohol).

Physical measurements including height and weight were made, and venous nonfasting blood samples were taken for measurement of biochemical and hematological variables. Aliquots of serum from the men in the seventh to 24th towns visited (n=5663) were stored at −20°C. Because of the influence that preexisting cardiovascular disease and diabetes mellitus may have on metabolic risk factor levels and physical activity, men with recall of physician diagnosis of stroke or CHD, subjects with known diabetes at screening, and men with asymptomatic hyperglycemia (glucose level, ≥11.1 mmol/L; ≥200 mg/dL) were excluded (n=441). After these exclusions, data were available for a group of 5222 men, the subjects of this study.

BIOLOGICAL MEASUREMENTS

Body mass index (BMI), calculated as weight divided by the square of height in meters, was used as an index of relative weight. Obesity is defined as a BMI of 28.0 or more, the top fifth of the distribution in the original 7735 men. Hematocrit was determined by means of an electronic particle counter (Coulter S; Coulter Electronics Ltd, Lytchett Matravers, England), which was calibrated daily (Coulter SC; Coulter Electronics Ltd).21 Heart rate was measured from the resting electrocardiogram.22

Blood pressure was recorded with a sphygmomanometer from the London School of Hygiene, London, England. Two successive recordings were taken, and the mean was used in the analysis with adjustment for observer variation within each town.23

All of the blood samples for determination of lipid levels were obtained in the nonfasting state between 8:30 AM and 6:30 PM. Detailed information on blood lipid levels (total cholesterol and HDL cholesterol).7,19 The role of insulin was not investigated. This article examines the relationship between physical activity and nonfasting insulin level, components of the insulin resistance syndrome, and other biological factors associated with the risk of type 2 diabetes or CHD. The purpose is to determine whether these factors mediated the relationship between physical activity and the incidence of CHD events and the incidence of type 2 diabetes during a 16.8-year follow-up.
golf, swimming, tennis, sailing, and digging. A total physical score was calculated for each man on the basis of the frequency and type (intensity) of physical activities. Scores assigned for each type of activity and its duration were based on the intensity and energy demands of the activities reported. This was based on the recommendations of a National Heart, Lung, and Blood Institute workshop and the Minnesota intensity codes. Physical activity at work was excluded from the score partly because few middle-aged men do physically demanding work and partly because such activities are not readily amenable to modification.

The total score for each man was not a measure of total time spent in physical activity but a relative measure of how much physical activity had been carried out or energy expended. The men were initially grouped into 6 broad categories on the basis of their total score: (1) inactive (score, 0-2; n=465); (2) occasional (score, 3-5; n=1498); regular walking or recreational activity only; (3) light (score, 6-8; n=1279); more frequent recreational activities, or sporting exercise less than once a week, or regular walking plus some recreational activity; (4) moderate (score, 9-12; n=842); cycling, or very frequent weekend recreational activities plus regular walking, or sporting activity once a week; (5) moderately vigorous (score, 13-20; n=746); sporting activity at least once a week or frequent cycling, plus frequent recreational activities or walking, or frequent sporting activities only; and (6) vigorous (score, ≥21; n=329); very frequent sporting exercise, or frequent sporting exercise plus other recreational activities.

The use of the physical activity score has been validated previously by means of heart rate and forced expiratory volume in 1 second in men free of preexisting CHD. Mean heart rate and forced expiratory volume in 1 second decreased significantly with increasing levels of physical activity, even after adjustment for potential confounders. We excluded 63 men who did not provide complete data on the physical activity questionnaire, leaving 5159 men for analysis. In the analysis, the moderately vigorous and vigorous categories were combined and 5 groups were used.

PRECERTIFIED UNDIAGNOSED CHD

Men with undiagnosed evidence of CHD were defined as those with no recall of a physician diagnosis of CHD but who had a response on the World Health Organization (Rose) questionnaire indicating angina or possible myocardial infarction, or electrocardiographic evidence of definite or possible myocardial ischemia or myocardial infarction.

FOLLOW-UP

All men were followed up for all-cause mortality, cardiovascular morbidity, and development of type 2 diabetes from the initial screening in January 1978 to July 1980 up to December 1995, a mean period of 16.8 years (range, 15.5-18.0 years), and follow-up was achieved for 99% of the cohort. Information on death was collected through the established “tagging” procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Evidence regarding nonfatal heart attacks and diabetes was obtained by reports from general practitioners, by biennial reviews of the patients’ notes through to the end of the study period, and from personal questionnaires to surviving subjects at the fifth and 12th years after initial examination. A nonfatal heart attack was diagnosed according to World Health Organization criteria, which included any report of myocardial infarction accompanied by at least 2 of the following: a history of severe chest pain, electrocardiographic evidence of myocardial infarction, and cardiac enzyme changes associated with myocardial infarction. A diagnosis of diabetes was not accepted on the basis of self-completed questionnaire data unless confirmed in the primary care records.

STATISTICAL METHODS

The Cox proportional hazards model was used to assess the effects of physical activity on the risk of CHD and type 2 diabetes incidence. Physical activity was fitted as a categorical variable for the 5 groups (none, occasional, light, moderate, and moderately vigorous/vigorous). In some of the analyses, tests for linear trend for physical activity were assessed by assigning quantitative values (1-5) for the 5 groups of physical activity and fitting physical activity as a continuous variable rather than as categorical variables. In the adjustment, age; BMI; heart rate; levels of γ-glutamyltransferase (GGT), urate, triglyceride, and HDL cholesterol; and diastolic blood pressure were fitted as continuous variables. Alcohol intake (5 levels: none, occasional, light, moderate, and heavy), smoking (5 levels: never, ex-smoker, and 1-19, 20, and ≥21 cigarettes per day), and social class (7 groups: I, II, III nonmanual, III manual, IV, V, and armed forces) were fitted as categorical variables. Direct standardization was used to obtain age-adjusted rates per 1000 person-years by using the study population as the standard. To determine the possible mediating factors, each biological or metabolic risk factor was fitted in turn to the multivariate model, which included age, BMI, smoking, social class, alcohol intake, and preexisting CHD. The validity of the proportional hazards assumption for these models was assessed by fitting a time-dependent explanatory factor X(t)=X(t), where X(t)=log(t) X physical activity levels. At each event time, subjects still alive just before each event time would have their X value changed accordingly. The test for trend over time in the hazard ratio was not statistically significant for any level of physical activity. Logistic regression was used to assess the odds of having elevated levels of the metabolic and biological factors, adjusting for confounders.

RESULTS

During the mean follow-up period of 16.8 years, there were 616 cases of major CHD events (fatal and nonfatal; 8.0/1000 person-years) and 196 incident cases of type 2 diabetes (2.6/1000 person-years) in the 5159 men free of diagnosed CHD, stroke, and diabetes. Figure 1 shows the relationship between physical activity and age-adjusted rates for CHD and type 2 diabetes. An inverse relationship was seen between physical activity
and CHD rates, with the lowest rates in men undertaking moderate levels of physical activity (test for trend, \( P < .001 \)). No further benefit was seen thereafter. For type 2 diabetes, age-adjusted rates decreased progressively with increasing levels of physical activity (test for trend, \( P < .001 \)).

**PHYSICAL ACTIVITY, LIFESTYLE CHARACTERISTICS, AND PREEXISTING CHD**

Physical activity was strongly and inversely associated with obesity, smoking, social class, and heavy drinking and with preexisting CHD (undiagnosed) (Table 1).

**PHYSICAL ACTIVITY AND METABOLIC RISK FACTORS**

Table 2 shows the relationship between physical activity and metabolic risk factors as well as with biological factors previously shown to be associated with CHD or type 2 diabetes, eg, hematocrit and GGT level, a possible marker for visceral fat. These relationships have been adjusted for lifestyle characteristics and preexisting CHD (undiagnosed). Physical activity was significantly related to HDL cholesterol level (positively), triglyceride, insulin, and urate levels (all negatively), and components of the insulin resistance syndrome, but was not associated with serum total cholesterol or serum glucose levels. Little association was seen with hematocrit, but a strong inverse association was seen with GGT level.

Although the differences in absolute mean levels of insulin, triglyceride, GGT, and HDL cholesterol between the physical activity groups were small, the reduction in the odds (risk) of having hyperinsulinemia, hypertriglyceridemia, low HDL cholesterol level, and high GGT level, defined as the top and bottom fifth of the distribution in the 5159 men, was substantial (Figure 2), even after adjustments for factors shown in Table 2. A moderate level of physical activity was associated with a 50% reduction in the risk of having an elevated GGT level, 40% reduction in risk of having hyperinsulinemia, 30% reduction in risk of hypertriglyceridemia, and a 25% reduction in risk of having low HDL cholesterol level. The reductions in risk of hyperuricemia and diastolic hypertension were small. To assess whether insulin determined these relationships, further adjustments were made for serum insulin level. The relationships between physical activity and urate and triglyceride levels were markedly attenuated after adjustment. Physical activity remained significantly associated with HDL cho-

**Table 1. Percentage of Men With Specific Lifestyle Characteristics and Preexisting Coronary Heart Disease (CHD) (Undiagnosed) According to Level of Physical Activity**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of Men</th>
<th>Test for Trend, ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (( \geq 28 \text{ kg/m}^2 ))</td>
<td>23.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smokers (current)</td>
<td>53.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Manual workers</td>
<td>65.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy drinking*</td>
<td>17.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Preexisting CHD (undiagnosed)</td>
<td>28.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Defined as 42 U/wk; greater than 60 g of alcohol per day.

Figure 1. Age-adjusted coronary heart disease (CHD) and type 2 diabetes event rate per 1000 person-years in 5159 men aged 40 to 59 years during an average follow-up of 16.8 years. The numbers above each bar represent number of events.
Physical activity is associated with many known CHD risk factors, including blood pressure (inversely) and HDL cholesterol level (positively), and attention has been drawn to their role as possible intermediate mechanisms. More recently, attention has focused on the role of insulin resistance. Hyperinsulinemia is associated with hypertriglyceridemia, low HDL cholesterol level, impaired glucose tolerance, and hypertension and more recently with serum uric acid level. Serum insulin levels have been used as an estimate of insulin sensitivity, and a significant independent relationship between hyperinsulinemia and risk of CHD has been reported from several large epidemiological studies. Exercise training is

**PHYSICAL ACTIVITY AND MAJOR CHD EVENTS**

Age-adjusted relative risk of CHD decreased significantly with occasional and light physical activity and was lowest in the moderately active men (Table 3, column A). Adjustments for age, lifestyle characteristics (smoking, alcohol, social class, and BMI), and preexisting CHD (undiagnosed) (column B) reduced the benefit in the higher activity groups (from light upward), but these levels remained significantly associated with reduced risk of CHD. To assess the influence of these biological factors on the relationship between physical activity and CHD, we examined the effects of additional adjustments for factors shown to be related to physical activity, ie, insulin and its associated metabolic factors (triglyceride, urate, and HDL cholesterol levels and diastolic blood pressure) as well as heart rate. Because of the particular interest in insulin, adjustment was made first for insulin (column C) and then, in addition, for the associated factors and heart rate (column D). Adjustment for insulin level made very little difference to the relationship. The additional adjustment for the associated factors and heart rate also made little further difference.

**PHYSICAL ACTIVITY AND TYPE 2 DIABETES**

The age-adjusted relative risk decreased progressively with increasing levels of physical activity (Table 4, column A). After adjustment for age, lifestyle characteristics, and preexisting CHD (column B), physical activity remained significantly and inversely associated with type 2 diabetes. In contrast to the effects on CHD risk, adjustment for insulin reduced the trend, although it remained significant (column C). Further adjustment for factors associated with insulin, ie, HDL cholesterol level, diastolic blood pressure, triglyceride level, and urate level, as well as heart rate reduced the trend further, and it was no longer significant (column D). Additional adjustment for GGT level reduced the benefit associated with higher levels of physical activity even further (column E). These factors appeared to account for about 40% of the reduction in risk of type 2 diabetes associated with moderately vigorous/vigorous levels of physical activity.

**INTERMEDIATE MECHANISMS**

The present study, based on 16.8 years’ mean follow-up, confirms the beneficial effects of physical activity on risk of both CHD and type 2 diabetes. Moderate levels of activity, which involve sporting activity once a week or frequent lighter-intensity activities, eg, walking, gardening, and do-it-yourself projects, are sufficient to produce a significant reduction in risk of both CHD and type 2 diabetes. Men who undertook moderately vigorous or vigorous levels of activity showed a slightly increased risk of CHD but not diabetes compared with the moderately active group. Shaper et al reported previously that this increased risk is seen for CHD but not for stroke, and that this excess risk appears to be confined to hypertensive men who are vigorously active. The mechanism of the excess risk is not clear, but it does not appear to be mediated through sudden cardiac death.

**COMMENT**

Physical activity is associated with many known CHD risk factors, including blood pressure (inversely) and HDL cholesterol level (positively), and attention has been drawn to their role as possible intermediate mechanisms. More recently, attention has focused on the role of insulin resistance. Hyperinsulinemia is associated with hypertriglyceridemia, low HDL cholesterol level, impaired glucose tolerance, and hypertension and more recently with serum uric acid level. Serum insulin levels have been used as an estimate of insulin sensitivity, and a significant independent relationship between hyperinsulinemia and risk of CHD has been reported from several large epidemiological studies. Exercise training is

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**Table 2. Physical Activity and Adjusted Mean Levels of Cardiovascular and Metabolic Risk Factors in Men With No Diagnosed CHD, Stroke, or Diabetes**

<table>
<thead>
<tr>
<th></th>
<th>Inactive</th>
<th>Occasional</th>
<th>Light</th>
<th>Moderate</th>
<th>Moderately Vigorous/Vigorous</th>
<th>Test for Trend, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>74.1</td>
<td>73.3</td>
<td>72.8</td>
<td>72.2</td>
<td>70.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>147.1</td>
<td>146.8</td>
<td>146.1</td>
<td>146.2</td>
<td>145.5</td>
<td>.09</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84.6</td>
<td>83.8</td>
<td>83.0</td>
<td>83.3</td>
<td>82.7</td>
<td>.003</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.23</td>
<td>6.30</td>
<td>6.31</td>
<td>6.23</td>
<td>6.26</td>
<td>.58</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.12</td>
<td>1.13</td>
<td>1.14</td>
<td>1.14</td>
<td>1.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.76</td>
<td>1.79</td>
<td>1.73</td>
<td>1.73</td>
<td>1.68</td>
<td>.007</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>94</td>
<td>86</td>
<td>82</td>
<td>80</td>
<td>79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.42</td>
<td>5.42</td>
<td>5.42</td>
<td>5.42</td>
<td>5.47</td>
<td>.36</td>
</tr>
<tr>
<td>Urate, µmol/L</td>
<td>357.9</td>
<td>359.8</td>
<td>357.3</td>
<td>360.3</td>
<td>352.3</td>
<td>.04</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.449</td>
<td>0.446</td>
<td>0.446</td>
<td>0.445</td>
<td>0.445</td>
<td>.05</td>
</tr>
<tr>
<td>GGT, g/L</td>
<td>16.9</td>
<td>16.4</td>
<td>15.9</td>
<td>15.0</td>
<td>14.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, social class, smoking, heavy drinking, and preexisting coronary heart disease (CHD) (undiagnosed). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; and GGT, γ-glutamyltransferase. To convert cholesterol and HDL-C to milligrams per deciliter, divide by 0.02586; to convert triglyceride to milligrams per deciliter, divide by 0.01129; to convert glucose to milligrams per deciliter, divide by 0.05551.
known to enhance insulin sensitivity,\textsuperscript{15,16} and it has been suggested that insulin resistance may be the mediating factor in the relationship between physical activity and CHD and type 2 diabetes.

In the present study, physical activity was significantly and inversely associated with serum insulin levels and with many of its components, ie, levels of HDL cholesterol, triglycerides, and urate and, to a lesser extent, diastolic blood pressure. The associations with insulin, triglyceride, HDL-C, and urate levels are consistent with the known finding that exercise training increases insulin sensitivity. The relationship with insulin showed a dose response, with levels decreasing progressively with increasing levels of physical activity. The decrease seen even at lighter levels of activity is consistent with recent findings from the Insulin Resistance Atherosclerosis Study showing that both vigorous and non-vigorous activities are associated with a significantly improved insulin sensitivity.\textsuperscript{36} The relationships between physical activity and triglyceride and urate appeared to be due to insulin, indicating that physical activity may act on these factors partly via effects on insulin metabolism. The Mauritius study\textsuperscript{18} also suggested that much of the effect of physical activity on lipoproteins (triglycerides and HDL cholesterol) is mediated via its effect on insulin and glucose metabolism. However, in the present study, the relationship between physical activity and HDL cholesterol level was independent of non-fasting insulin levels. Physical activity has consistently been shown to be associated with increased levels of HDL cholesterol, and the present study indicates that high intensity levels are not required to obtain a significant increase in HDL cholesterol level. The reduction in risk of having a low HDL cholesterol level was seen at light levels of physical activity and is consistent with the concept that HDL cholesterol level is related more to the

Figure 2. Relative risks (adjusted odds ratios) of hyperinsulinemia, hypertriglyceridemia, low level of high-density lipoprotein cholesterol (HDL-C), high diastolic blood pressure (DBP), hyperuricemia, and high level of y-glutamyltransferase (GGT) according to levels of physical activity, adjusted for age, body mass index, social class, smoking, heavy drinking, and preexisting coronary heart disease (undiagnosed). X indicates adjusted in addition for serum insulin level.

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amount of exercise than to aerobic capacity per se, and supports the suggestion that frequency of exercise may be particularly important in influencing HDL cholesterol level. A strong and graded relationship was also seen with GGT level, thought to be a marker for visceral fat, hepatic steatosis, and hepatic insulin resistance. This supports the hypothesis that the benefit of physical activity on type 2 diabetes is mediated through increased insulin sensitivity. Although moderate activity levels and above were still associated with reduced risk of type 2 diabetes after full adjustment (Table 4, column E), this difference compared with inactivity was nonsignificant. The reduced risk still seen is likely to reflect residual confounding, and it is possible that more precise measures of insulin would have attenuated the risk further. Furthermore, physical training has been shown to influence visceral adiposity more than BMI, and it could be argued that the risk of type 2 diabetes would be further attenuated if we had more specific measures of body fat distribution.

**PHYSICAL ACTIVITY, INSULIN RESISTANCE SYNDROME, AND TYPE 2 DIABETES**

Most studies have shown a beneficial influence of physical activity on risk of type 2 diabetes independent of age, obesity, body fat distribution, family history, and conventional cardiovascular risk factors, eg, blood pressure and total cholesterol level, and some have found the relationship to be independent of levels of HDL cholesterol, triglycerides, and glucose. Most studies have not adjusted for all of these factors simultaneously, and we are not aware of any prospective study to date that has examined the role of insulin as a mediating factor in the relationship between physical activity and type 2 diabetes. The present findings indicate that the protective effect of physical activity on type 2 diabetes can be largely attributed to the favorable influence of physical activity on the various components of the insulin resistance syndrome and to the concentration of GGT, a possible marker of hepatic insulin resistance. This supports the hypothesis that the benefit of physical activity on type 2 diabetes is mediated through increased insulin sensitivity. Although moderate activity levels and above were still associated with reduced risk of type 2 diabetes after full adjustment (Table 4, column E), this difference compared with inactivity was nonsignificant. The reduced risk still seen is likely to reflect residual confounding, and it is possible that more precise measures of insulin would have attenuated the risk further. Furthermore, physical training has been shown to influence visceral adiposity more than BMI, and it could be argued that the risk of type 2 diabetes would be further attenuated if we had more specific measures of body fat distribution.

**PHYSICAL ACTIVITY, INSULIN, AND RISK OF CHD**

In contrast to type 2 diabetes, insulin and its components appear to play a very minor role in the relationship between physical activity and CHD. The use of non-fasting insulin measurements, adjusted for time of sampling, has almost certainly increased the amount of random error or “noise” in the data compared with the use of insulin measured under more rigorous conditions. All measurements of insulin in epidemiological studies are beset by problems of high within-subject variability relative to between-subject variability, and it is likely that differences in this regard are small between fasting postload and nonfasting samples (adjusted for time of sampling). Despite this constraint, previous reports from
The British Regional Heart Study have shown the associations between nonfasting insulin level and cardiovascular risk factors, such as BMI, blood lipid levels, and blood pressure, to be consistent with those reported with fasting and postload insulin levels in other studies. Furthermore, the correlations between insulin and these risk factors were similar irrespective of time of sampling. In a previous report from this study that presented correlation coefficients between insulin and biological risk factors, the interrelations with biological risk factors were virtually identical to those reported from a population-based study in Eastern Finland in which fasting and 2-hour plasma insulin values were measured. This strongly suggests that the use of nonfasting insulin level in the present investigation is not associated with systematic measurement error. Elevated serum insulin level has been shown to be associated with increased risk of both type 2 diabetes and CHD, and insulin and its associated metabolic factors appear to explain a large proportion of the relationship between physical activity and type 2 diabetes but not between physical activity and CHD. Thus, it is unlikely that the lack of effect of insulin on the physical activity–CHD relationship simply results from the use of nonfasting insulin.

The Honolulu Heart study suggested that the beneficial effect of physical activity on the risk of CHD is mediated through the effect of physical activity on other cardiovascular risk factors, such as blood pressure, BMI, and total cholesterol level. That study, based on one physical activity measurement at baseline and 23 years of follow-up, showed a much weaker relationship than when shorter follow-up (12 years) was used. There is evidence that physical activity has to be current and continued to confer benefit, and it is highly likely that a fair proportion of the high-activity group at baseline is increasingly inactive with the passage of time.

Although our physical activity data are based on one measurement in time, an examination of changes in physical activity reported at screening and 12 to 14 years later in men with no diagnosed cardiovascular disease showed that, although a proportion (22%) of men who were at least lightly active became inactive or occasionally active 12 to 14 years later, the majority of men who were at least moderately active at baseline remained at least moderately active 12 to 14 years later. Our findings in the present study, based on 16.8 years of follow-up, showed that the benefit of physical activity for CHD was independent of established CHD risk factors, eg, blood pressure and levels of HDL cholesterol, triglycerides, and insulin. Thus, the protective effect of physical activity must act via other mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms. Since exercise has to be current and continued to confer protection, this suggests the influence of acute mechanisms.

In addition, regular physical activity is associated with higher levels of physical fitness, which in turn are associated with decreased mortality risk.

The relationship between physical activity and type 2 diabetes appears to be mediated by serum true insulin level and components of the insulin resistance syndrome. However, these factors do not appear to explain the inverse relationship between physical activity and CHD, and it must be presumed that other mechanisms are operating.

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REFERENCES

CONCLUSIONS

The relationship between physical activity and type 2 diabetes appears to be mediated by serum true insulin.


