Low Levels of Leisure-Time Physical Activity and Cardiorespiratory Fitness Predict Development of the Metabolic Syndrome

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OBJECTIVE — Little is known about the association of leisure-time physical activity (LTPA) and cardiorespiratory fitness with development of the metabolic syndrome, which predisposes diseases such as diabetes and atherosclerosis. We studied the associations of LTPA and cardiorespiratory fitness with development of the metabolic syndrome (World Health Organization [WHO] and the National Cholesterol Education Program [NCEP] definitions).

RESEARCH DESIGN AND METHODS — LTPA over the previous 12 months, $V\text{O}_{2\max}$ ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and cardiovascular and metabolic risk factors were assessed in a population-based cohort of 612 middle-aged men without the metabolic syndrome.

RESULTS — At the 4-year follow-up, 107 men had metabolic syndrome (WHO definition). Men engaging in >3 h/week of moderate or vigorous LTPA were half as likely as sedentary men to have the metabolic syndrome after adjustment for major confounders (age, BMI, smoking, alcohol, and socioeconomic status) or potentially mediating factors (insulin, glucose, lipids, and blood pressure), especially in high-risk men. Vigorous LTPA had an even stronger inverse association, particularly in unfit men. Men in the upper third of $V\text{O}_{2\max}$ were 75% less likely than unfit men to develop the metabolic syndrome, even after adjustment for major confounders. Adjustment for possible mediating factors attenuated the association. Associations of LTPA and $V\text{O}_{2\max}$ with development of the metabolic syndrome, as defined by the NCEP, were qualitatively similar.

CONCLUSIONS — In particular, high-risk men engaging in currently recommended levels of physical activity were less likely to develop the metabolic syndrome than sedentary men. Cardiorespiratory fitness was also strongly protective, although possibly not independent of mediating factors.

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Abbreviations: ACSM, American College of Sports Medicine; CDC, Centers for Disease Control and Prevention; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; LTPA, leisure-time physical activity; MET, metabolic equivalent; NCEP, National Cholesterol Education Program; OR, odds ratio; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In prospective cohort studies, higher levels of physical activity have quite consistently protected against the development of diabetes and cardiovascular disease (1–5), conditions that are commonly associated with the metabolic syndrome. Recently, lifestyle interventions, including regular physical activity, have been shown to reduce the incidence of diabetes by more than half in persons with impaired glucose tolerance (IGT) (6,7). Although the pathogenesis of the metabolic syndrome remains unclear, the metabolic syndrome is in its early stages, characterized by mild and varying degrees of abnormalities of insulin, glucose and lipid metabolism, hypertension, and overweight, which if unchecked, may progress over years to overt diseases such as diabetes and atherosclerosis in its various manifestations (8). Because of the current epidemic of overweight and sedentary lifestyle worldwide, the metabolic syndrome poses a serious and growing problem for clinicians and public health officials alike (9).

Physical activity may protect against diabetes and cardiovascular disease in part through components of the metabolic syndrome. In intervention studies, physical exercise has, in variable degrees and at least in the short term, decreased weight and visceral fat accumulation (10–13), increased HDL cholesterol and decreased triglyceride levels (13–15), decreased blood pressure (13,16), and improved insulin sensitivity (10–12). These changes have often occurred independent of weight loss, although it is not completely clear how much of these favorable effects are independent of weight loss and changes in body composition (17). Based on the intervention and epidemiological evidence, the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) have jointly published recommendations that adults engage in at least 30 min of moderate physical activity on most, and preferably all, days of the week (13).

Although strong evidence suggests that physical exercise favorably affects individual components of the metabolic syndrome, little evidence exists showing that physical activity prevents the metabolic syndrome itself. Such information is necessary for healthcare providers and public health policy makers seeking to prevent the consequences of the metabolic syndrome already at an early phase. An inverse association of physical activity and cardiorespiratory fitness with the number of components of the metabolic syndrome has been shown in middle-aged men (18,19). The cross-sectional nature of these studies do not, however, allow inference of causality.

Despite the abundant epidemiological and experimental research that has been published on the metabolic syndrome, definitions of the components of the metabolic syndrome and the various cutoffs for those components have widely varied (8). The World Health Organization (WHO) Consultation for the Classification of Diabetes and its Complications recently published a working definition of the metabolic syndrome as insulin resistance, IGT, or type 2 diabetes and two of the following: abdominal obesity, dyslipidemia, hypertension, and microalbuminuria (20). The National Cholesterol Education Program (NCEP) has recently defined the metabolic syndrome as three or more of the following: elevated glucose levels, high triglyceride levels, low HDL levels, elevated blood pressure, and abdominal obesity (21). This definition is clinically oriented, based on features of the metabolic syndrome rather than insulin resistance itself, as in the case of the WHO definition.

In this study, we investigated the associations of lifestyle and structured leisure-time physical activity (LTPA) of various intensities and cardiorespiratory fitness with development of the metabolic syndrome as defined by the WHO and the NCEP over 4 years in middle-aged nondiabetic men from Eastern Finland without the metabolic syndrome at baseline.

RESEARCH DESIGN AND METHODS

Participants

The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a prospective population-based study (22). The study population was a random age-stratified sample of men living in eastern Finland who were 42, 48, 54, or 60 years old at baseline. The Research Ethics Committee of the University of Kuopio approved the study. All subjects gave written informed consent.

The KIHD 4-year follow-up study included 1,038 subjects who had undergone carotid ultrasound examination during the original study, as described in detail previously (22,23). Men who had the metabolic syndrome or diabetes at baseline or for whom data for defining the metabolic syndrome were incomplete were excluded, leaving 612 and 771 men for analyses of the development of the metabolic syndrome as defined by the WHO and the NCEP, respectively.

Metabolic syndrome

The metabolic syndrome was defined as the presence of hyperinsulinemia (fasting insulin levels in the top 25% of the nondiabetic population), impaired fasting glycemia (IFG), or diabetes and at least two of the following: adiposity (waist-to-hip ratio >0.90 or BMI ≥30 kg/m^2), dyslipidemia (triglyceride level ≥1.70 mmol/l or HDL level <0.9 mmol/l), and hypertension (blood pressure ≥140/90 mmHg or current use of antihypertensive medication) (20). Diabetes was defined as fasting blood glucose ≥6.1 mmol/l or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment (20). IFG was defined as fasting blood glucose 5.6–6.0 mmol/l (20).

The WHO definition was meant to facilitate research on the metabolic syndrome and aid comparability between studies rather than serve as a strict definition. The WHO consultation recommended that insulin resistance be measured by the euglycemic-hyperinsulinemic clamp and that IGT be used in the definition of the metabolic syndrome (20). Because particularly clamp testing is not generally feasible in epidemiological studies, use of fasting insulin concentrations to estimate insulin resistance and IFG as a substitute for IGT was used, as has been proposed previously (24). Inclusion of microalbuminuria as a core component of the metabolic syndrome is controversial (24,25). Moreover, microalbuminuria is uncommon in nondiabetic subjects (26). Therefore, we did not include microalbuminuria (24). The WHO definition modified in this way has been validated (27).

As an additional check on the robustness of our analyses, we repeated the main analyses using the recent NCEP definition of the metabolic syndrome (21). The metabolic syndrome was defined as three or more of the following: fasting blood glucose level ≥5.6 mmol/l, serum triglyceride level ≥1.7 mmol/l, HDL level <1.0 mmol/l, blood pressure ≥130/85 mmHg or use of antihypertensive medication, and waist girth >94 cm. We used the lower level of abdominal obesity (94 cm) suggested in the NCEP definition, because the metabolic syndrome with waist >94 cm detected diabetes better during follow-up than that with waist girth >102 cm (27).

Assessment of physical activity

The validated KIHD 12-month Leisure-Time Physical Activity Questionnaire was used as described previously (3,28). This is a detailed quantitative questionnaire assessing the duration, frequency, and mean intensity of the most common lifestyle and structured LTPA of middle-aged Finnish men as recalled over the previous 12 months. Low-intensity LTPA was defined as <4.5 metabolic equivalents (METs) (1 MET is defined as metabolic expenditure at rest, corresponding to an oxygen uptake of 3.5 ml O_2/kg). Common low-intensity LTPA includes walking, yard work, fishing or hunting, and berry or mushroom gathering. Moderate- and high-intensity lifestyle and conditioning LTPA was defined as ≥4.5 METs (11). Common moderate- or high-intensity LTPA included brisk walking, skiing, jogging, swimming, bicycling, ball games, and forestry (chopping wood, cutting trees, or clearing brush, etc.). The cutoff ≥7.5 METs for vigorous physical activity included activities commonly considered vigorous (e.g., skiing, jogging, ball sports, or forestry) at the subjective intensities at which they were practiced. The durations (in minutes/week) of total, low-intensity, moderate- and high-intensity, and high-intensity LTPA were calculated.

Assessment of cardiorespiratory fitness

A graded symptom-limited maximal exercise test was performed on an electrically braked cycle ergometer (model 400L; Medical Fitness Equipment, Mearn, the

Table 1—*Baseline characteristics of the 107 men who developed the metabolic syndrome during follow-up and the 505 men who did not*

	At 4-year-follow-up		
	Without metabolic syndrome	With metabolic syndrome	*P*
N	505	107	
Age (years)	50.9 ± 6.6	52.7 ± 6.1	0.005*
Cardiovascular disease (%)	9	44	0.001
Smokers (%)	33	31	0.70
Use of blood pressure medication (%)	11	31	<0.001
Systolic blood pressure (mmHg)	128.8 ± 14.0	135.3 ± 15.6	<0.001
Diastolic blood pressure (mmHg)	85.6 ± 9.7	90.6 ± 8.9	<0.001
BMI (kg/m^2)	25.5 ± 3.2	28.0 ± 4.4	<0.001
Waist-to-hip ratio	0.92 ± 0.06	0.96 ± 0.05	<0.001
Serum HDL cholesterol (mmol/l)	1.36 ± 0.30	1.23 ± 0.26	<0.001
Serum triglycerides (mmol/l)	1.14 ± 0.56	1.48 ± 0.96	<0.001
Fasting blood glucose (mmol/l)	4.4 ± 0.4	4.6 ± 0.4	0.002
Fasting serum insulin (pmol/l)	56.3 ± 18.1	73.6 ± 22.9	<0.001
$V\text{O}_{2\text{max}}$ (ml · kg^{-1} · min^{-1})	33.6 ± 7.9	28.5 ± 7.2	<0.001
Total LTPA (min/week)	393 (231–618)	320 (164–501)	0.006
LTPA <4.5 METs (min/week)	195 (84–370)	143 (58–303)	0.032
LTPA ≥4.5 METs (min/week)	147 (63–255)	121 (43–211)	0.030
LTPA ≥7.5 METs (min/week)	31 (7–91)	12 (0–42)	<0.001

Data are means ± SD, except for LTPA variables, which are presented as median (interquartile range). *Mann-Whitney *U* test.

Netherlands). Workload was increased linearly by 20 W/min. $V\text{O}_{2\text{max}}$ was measured directly with breath-by-breath respiratory gas-exchange analysis (Medical Graphics 2001; Medical Graphics, St. Paul, MN), as previously described (3). $V\text{O}_{2\text{max}}$ was defined as the peak or plateau in oxygen uptake.

Assessment of components of the metabolic syndrome

Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley, U.K.). The measurement protocol included, after supine rest of 5 min, three measurements while supine, one measurement while standing, and two measurements while sitting at 5-min intervals. The mean of all six measurements was used as the systolic and diastolic blood pressure.

BMI was computed as weight/height squared. Waist circumference was taken as the average of two measurements taken after inspiration and after expiration (mean difference between the two measurements ~1.5 cm) at the midpoint between the lowest rib and the iliac crest. Waist-to-hip ratio was defined as waist girth/hip circumference measured at the trochanter major.

Subjects were asked to fast and to refrain from smoking for 12 h and to avoid alcohol intake for 3 days before blood sampling. Blood glucose level was measured at baseline using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. The serum samples for insulin determination were stored at −80°C. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark) (29). LDL and HDL fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglyceride levels were measured enzymatically.

Medical history and medications, family history of diseases, smoking (30), alcohol consumption (4), and adult socioeconomic status (31) were also assessed.

Statistical analysis

Differences in baseline clinical and biochemical characteristics between men who developed the metabolic syndrome during follow-up and those who did not were tested for statistical significance with Student's *t* test, Mann-Whitney *U* test, or χ^2 test. The association of LTPA and cardiorespiratory fitness with the development of the metabolic syndrome during follow-up was estimated using logistic regression adjusting for potential confounding or mediating factors. Indexes of LTPA and cardiorespiratory fitness were categorized into thirds for the logistic regression analyses (except for moderate-to-vigorous LTPA, which was categorized based on minutes/week according to the CDC/ACSM recommendations), although results were similar using continuous variables (not shown). The covariates for the logistic regression models were forced into the model, although results were similar when using a stepwise model. Durations of LTPA (in minutes/week) are presented as medians (interquartile ranges); other data are presented as means ± SD or simple percentages. Triglyceride and insulin concentrations and durations of LTPA were corrected for skewing using log transformation but are presented using untransformed values. Significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 10.0 for Windows (Chicago, IL).

RESULTS

Baseline measures

The 107 men in whom the metabolic syndrome developed by the end of the 4-year follow-up were heavier and more hypertensive, dyslipidemic, and hyperinsulinemic than the 505 men who did not already have the metabolic syndrome at baseline (Table 1). They also had slightly higher blood glucose levels and higher prevalence of cardiovascular disease.

Approximately 25% of the men engaged in ≤60 min/week of at least moderate LTPA (≥4.5 METs) over the previous year. Nearly 40% roughly met the ACSM and Surgeon General's recommendations for physical activity (at least 30 min of moderate-intensity exercise on most days of the week, calculated here as >3 h/week). Men in whom the metabolic syndrome did not develop had a higher $V\text{O}_{2\text{max}}$ and engaged in more LTPA, especially vigorous LTPA.

Baseline age-adjusted partial correlations

Moderate and especially vigorous physical activity, but not low-intensity LTPA, was correlated with cardiorespiratory fitness (age-adjusted correlation of $V\text{O}_{2\text{max}}$ with LTPA <4.5 METs, $r = 0.01$, $P =$

Table 2—*ORs for the development of the metabolic syndrome according to categories of baseline LTPA and cardiorespiratory fitness*

	Tertiles	Model 1*	Model 2†	Model 3‡	Model 4§
Total LTPA (min/week)					
<270 min/week	1	1	1	1	1
270–486 min/week	2	0.72 (0.43–1.19)	0.66 (0.38–1.15)	0.73 (0.44–1.22)	0.83 (0.45–1.52)
≥487 min/week	3	0.52 (0.30–0.89)	0.55 (0.31–0.98)	0.53 (0.31–0.92)	0.54 (0.28–1.04)
Trend (*P*)		0.055	0.10	0.073	0.18
Low-intensity LTPA (<4.5 METs, min/week)					
<111 min/week	1	1	1	1	1
111–270 min/week	2	0.86 (0.52–1.42)	0.93 (0.54–1.60)	0.90 (0.54–1.49)	0.97 (0.52–1.79)
≥271 min/week	3	0.60 (0.35–1.03)	0.62 (0.35–1.10)	0.61 (0.35–1.05)	0.66 (0.34–1.28)
Trend (*P*)		0.17	0.23	0.20	0.41
Moderate and vigorous LTPA (≥4.5 METs, min/week)					
≤60 min/week		1	1	1	1
61–180 min/week		0.82 (0.49–1.37)	0.74 (0.42–1.30)	0.82 (0.48–1.38)	0.86 (0.46–1.60)
≥18 min/week		0.52 (0.30–0.89)	0.52 (0.29–0.92)	0.52 (0.30–0.90)	0.55 (0.29–1.04)
Trend (*P*)		0.047	0.078	0.058	0.16
Vigorous LTPA (≥7.5 METs, min/week)					
<10 min/week	1	1	1	1	1
10–59 min/week	2	0.64 (0.39–1.05)	0.58 (0.34–0.98)	0.65 (0.39–1.08)	0.60 (0.33–1.09)
≥60 min/week	3	0.37 (0.21–0.65)	0.32 (0.18–0.59)	0.37 (0.21–0.66)	0.36 (0.19–0.70)
Trend (*P*)		0.002	0.001	0.003	0.009
$V\text{O}_{2\text{max}}$ (ml · kg^{-1} · min^{-1})					
≤28.9	1	1	1	1	1
29.0–35.6	2	0.52 (0.31–0.86)	0.59 (0.34–1.01)	0.53 (0.31–0.89)	0.84 (0.45–1.56)
≥35.7	3	0.24 (0.13–0.47)	0.36 (0.18–0.73)	0.25 (0.13–0.49)	0.70 (0.31–1.58)
Trend (*P*)		<0.001	0.014	<0.001	0.69

Data are OR (95% CI). *Adjusted for age category; †adjusted for age category and BMI; ‡adjusted for age category, BMI, adult socioeconomic status, presence of cardiovascular disease, smoking (not at all, 1–19 cigarettes per day, or 20 or more cigarettes per day), and alcohol consumption (abstainers, low intake, and high intake according to grams/week consumption); §adjusted for age category, BMI, waist-to-hip ratio, use of antihypertensive medications, systolic and diastolic blood pressure, and concentrations of HDL, triglycerides insulin, glucose levels, and family history of diabetes.

0.81; with LTPA ≥4.5 METs, $r = 0.24$, $P < 0.001$; with LTPA ≥7.5 METs, $r = 0.40$, $P < 0.001$).

Association of LTPA with development of the metabolic syndrome

In logistic regression analyses adjusting only for age (model 1), men with duration of total LTPA in the upper third were less likely to develop the metabolic syndrome than men whose duration of total LTPA was in the lower third (Table 2). Similarly, men engaging in >3 h a week of LTPA ≥4.5 METs were 48% less likely to develop the metabolic syndrome than sedentary men (≤60 min moderate intensity exercise/week). At least 60 min of vigorous LTPA seemed to reduce the likelihood to develop the metabolic syndrome by nearly two thirds. Although duration of low-intensity LTPA in the upper third seemed to decrease the likelihood of developing the metabolic syndrome by 40%, the association was not significant.

Odds ratios (ORs) for total LTPA, LTPA ≥4.5 METs, and LTPA ≥7.5 METs for development of the metabolic syndrome were not attenuated in logistic regression models adjusting for age and BMI (model 2) and for age, BMI, and other potentially confounding variables (model 3, Table 2). The ORs also remained virtually unchanged after adjustment for potentially mediating variables included in the definition of or related to the metabolic syndrome (model 4, Table 2). The 95% CIs widened, however, and the associations for total LTPA and LTPA ≥4.5 METs were no longer significant. In contrast, men participating in ≥60 min vigorous exercise/week were still nearly two thirds less likely to develop the metabolic syndrome than sedentary men ($P = 0.009$ for the trend).

Inclusion of low-intensity LTPA or $V\text{O}_{2\text{max}}$ as a continuous variable in the regression models had little effect on the ORs for moderate and vigorous LTPA (not shown). Exclusion of smokers or men with cardiovascular disease at baseline also had no qualitative effect on the associations, although some of the associations were no longer significant because of reduced statistical power.

Association of physical activity with development of the metabolic syndrome in high-risk men

Moderate and vigorous LTPA seemed to be especially effective in decreasing the likelihood of developing the metabolic syndrome in a particularly high-risk group of 286 men (hyperinsulinemia at baseline or two or more of the following: adiposity, dyslipidemia, or hypertension). The OR (95% CI) was 0.45 (0.22–0.94) for LTPA ≥4.5 METs (>3 h/week versus ≤60 min/week) and 0.25 (0.11–0.55) for LTPA ≥ 7.5 METs, upper versus lower third (model 4).

Associations of cardiorespiratory fitness with development of the metabolic syndrome

Men with high cardiorespiratory fitness were nearly two-thirds less likely to develop the metabolic syndrome in models

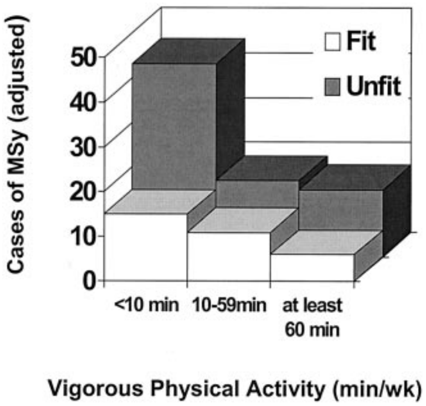

Figure 1—*The adjusted number of cases of the metabolic syndrome (MSy) at the 4-year follow-up according to duration (minutes/week) of vigorous LTPA in fit and unfit men. In unfit men,* P *for the most active versus least active category was 0.022,* P *for the trend was 0.025. The association in fit men was not significant, presumably because of the low incidence.*

adjusting only for age (Table 2). Importantly, little or no attenuation in the ORs was seen when adjusting for age and BMI or further for other potentially confounding variables (model 3). Extensive adjustment for variables closely associated with the metabolic syndrome (model 4) attenuated the association, however, suggesting that much of the association of cardiorespiratory fitness with development of the metabolic syndrome is mediated through these variables.

We stratified the men into low and high $V\text{O}_{2\text{max}}$ groups by age-group median $V\text{O}_{2\text{max}}$ to examine whether the association between vigorous LTPA and development of the metabolic syndrome is modified by cardiorespiratory fitness (Fig. 1). Case numbers are the actual case numbers by cardiorespiratory fitness level (divided into high- and low-fitness groups by age-group median maximal oxygen consumption) and adjusted over categories of duration of physical activity for numbers of men per category, age category, BMI, waist-to-hip ratio, family history of diabetes, use of antihypertensive medications, systolic and diastolic blood pressure, and concentrations of HDL, triglycerides, insulin, and glucose. It is clear that men who are less fit and sedentary represent a high-risk group for development of the metabolic syndrome, with a sevenfold increased likelihood of developing the metabolic syndrome compared with fit, active men.

Moderate or vigorous LTPA and cardiovascular fitness and the metabolic syndrome as defined by the NCEP

Of the 771 men who did not have the metabolic syndrome as defined by the NCEP or diabetes at baseline, 215 men had the metabolic syndrome at the 4-year follow-up. After adjustment for major potentially confounding factors (model 3), LTPA reduced the likelihood for development of the metabolic syndrome: the OR (95% CI) was 0.63 (0.41–0.97) for LTPA ≥4.5 METs (>3 h/week versus ≤ 60 min/week) and 0.45 (0.29–0.70) for LTPA ≥7.5 METs, upper versus lower third. In analyses adjusting for potentially mediating variables (model 4), the OR (95% CI) was 0.60 (0.37–0.99) for LTPA ≥4.5 METs (>3 h/week versus ≤60 min/week) and 0.48 (0.29–0.77) for LTPA ≥7.5 METs, upper versus lower third.

After adjustment for major potentially confounding factors (model 3), the OR (95% CI) was 0.27 (0.15–0.48) for development of the metabolic syndrome for $V\text{O}_{2\text{max}}$, upper third versus lower third. In analyses adjusting for potentially mediating variables (model 4), the OR (95% CI) for $V\text{O}_{2\text{max}}$, upper versus lower third, was 0.45 (0.23–0.88).

CONCLUSIONS — In what is, to our knowledge, the first study reporting the association of physical activity with the development of the metabolic syndrome, moderate and vigorous LTPA decreased the risk of the metabolic syndrome as defined by an adaptation of the WHO definition by up to nearly two-thirds in this population-based cohort of middle-aged men, even after extensive adjustment for potential mediating and confounding factors, especially in high-risk men. Moreover, findings were qualitatively similar, even when using two rather different definitions of the metabolic syndrome, one based heavily on insulin resistance or hyperinsulinemia (WHO) (20) and the other only on features related to insulin resistance (NCEP) (21). Cardiorespiratory fitness was also inversely associated with development of the metabolic syndrome independently of obesity and other important confounding factors.

The CDC-ACSM physical activity guidelines recommend that all adults engage in at least 30 min of moderate-intensity exercise per day (13). Moreover, the report emphasized "lifestyle" activity. Our findings suggest that men complying with the CDC-ACSM recommendations (here interpreted as >3 h/week of structured or lifestyle physical activity of ≥4.5 METs) decrease the risk of developing the metabolic syndrome by about one-half compared with men engaging in no more than 60 min of moderate exercise/week. Of importance, this association was independent of BMI and other potential confounders such as cardiovascular disease, smoking, and current socioeconomic status. When additional adjustment for potentially mediating factors, such as baseline insulin, glucose, lipid, and blood pressure levels, the 95% CIs widened such that the association was no longer significant in the entire cohort. In a high-risk subgroup of men with either baseline hyperinsulinemia or two or more features of the metabolic syndrome (hypertension, dyslipidemia, or overall or abdominal obesity), however, the protective effect of moderate or vigorous physical activity was significant even when adjusting for potentially mediating factors.

More dramatic reductions in risk were accrued by men engaging in ≥60 min vigorous activity/week compared with sedentary men. The decrease in likelihood of the metabolic syndrome in men engaging in regular moderate and vigorous exercise was also independent of low-intensity physical activity and cardiorespiratory fitness. These overall results are consistent with a previous cross-sectional study showing an age- and BMI-adjusted association between the metabolic syndrome as defined by the number of characteristics of the metabolic syndrome and physical activity (18) and another study using factor analysis in which a crude estimate of physical activity correlated inversely ($r = -0.25$) with the insulin resistance factor (31).

Low-intensity LTPA tended to decrease the likelihood of developing the metabolic syndrome. The associations were not statistically significant, perhaps because of a lack of statistical power. The volumes (>270 min/week) at which low-intensity LTPA tended to confer protection were considerably higher, however. From a clinical standpoint, such levels of exercise for sedentary persons are probably not practical, although substantial amounts of low-intensity LTPA could be achieved with successful adoption of an "active" lifestyle (e.g., substitution of low-intensity recreational activity or yard work for watching television, commuting by bike or foot to work, etc.). Low-intensity LTPA has consistently been less strongly associated with most chronic disease end points than moderate or vigorous exercise (1,4,13) but may have other important functions, e.g., weight control after weight loss in the obese (33).

Accurate assessment of habitual LTPA is problematic in epidemiological studies. Although data entry for the validated KIHD 12-month Leisure-Time Physical Activity Questionnaire (28) is time-intensive, the questionnaire provides detailed information on frequency, duration, and intensity of physical activity as recalled for the preceding 12 months. The rather high age-adjusted correlation of cardiorespiratory fitness with duration of vigorous LTPA, and conversely, absence of such a correlation with low-intensity physical activity are evidence for the validity of the questionnaire. When readministered 12 months later, LTPA in the KIHD questionnaire was quite repeatable (intraclass correlation coefficient 0.58, reflecting both the variability inherent in the questionnaire and that of LTPA itself) (28). The KIHD 12-month LTPA questionnaire seems to quantify LTPA well enough to allow for evaluation of current physical activity recommendations with respect to the metabolic syndrome. Even so, the associations in this study between LTPA and development of the metabolic syndrome are probably underestimations because of the inherent imprecision of physical activity questionnaires.

Men with $V\text{O}_{2\text{max}}$ in the upper third were 65–75% less likely to develop the metabolic syndrome than those in the lower third, even after adjustment for important confounding factors such as age, BMI, cardiovascular disease, smoking, and current socioeconomic status. The benefit of cardiorespiratory fitness was substantially attenuated after adjustment for other potential mediating factors such as blood pressure, triglyceride, and HDL cholesterol, insulin, and glucose levels. Directly measured or estimated $V\text{O}_{2\text{max}}$ has been consistently associated with many components of the metabolic syndrome, including insulin resistance, serum HDL, triglyceride levels, and blood pressure (4,18,19,32,34). Our findings suggest that high cardiorespiratory fitness is strongly protective against the metabolic syndrome, but that the benefit may be largely mediated by components of or closely related to the metabolic syndrome. Interestingly, findings were qualitatively similar, even when using the NCEP definition of the metabolic syndrome, which is based only on features related to insulin resistance (21). Despite marked attenuation of the strong inverse association of fitness with the development of the metabolic syndrome by the NCEP definition when adjusting for potentially mediating factors, the association remained significant. Although moderate and vigorous physical activity is an important determinant of $V\text{O}_{2\text{max}}$, a strong genetic component is also present (35). This raises the question of whether physical activity has similar effects in fit and unfit individuals.

Men who were both less fit and sedentary represented a high-risk group, with a sevenfold increased likelihood of developing the metabolic syndrome compared with fit men engaging in at least 60 min of vigorous activity weekly. Even modest amounts of vigorous physical activity in less fit men seemed to dramatically decrease the likelihood of developing the metabolic syndrome, even though active but unfit men were still ~2.5-fold more likely to develop the metabolic syndrome than active fit men. From a clinical perspective, measurement of $V\text{O}_{2\text{max}}$ in sedentary men may provide an efficient means to target even individuals with relatively few metabolic risk factors who may benefit from more intensive interventions including lifestyle or structured physical exercise in the prevention of the metabolic syndrome and its consequences.

Compliance with the current CDC-ACSM recommendations for physical activity markedly decreased the likelihood for development of the metabolic syndrome during the 4-year follow-up in this population-based cohort of middle-aged men, especially in high-risk groups. Vigorous LTPA provided additional benefits. Cardiorespiratory fitness was also strongly inversely associated with development of the metabolic syndrome, although possibly not independently of mediating factors. These findings support the CDC-ACSM recommendations for regular physical activity in the prevention of the metabolic syndrome and suggest that intervention at an early phase in even relatively low-risk men may dramatically reduce the risk for development or progression of metabolic disturbances that eventually culminate in chronic and progressive diseases such as diabetes and atherosclerosis.

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