Does the Association of Habitual Physical Activity With the Metabolic Syndrome Differ by Level of Cardiorespiratory Fitness?

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OBJECTIVE — Cardiovascular fitness ($V\text{O}_{2max}$) and physical activity are both related to risk of metabolic disease. It is unclear, however, whether the metabolic effects of sedentary living are the same in fit and unfit individuals. The purpose of this study was, therefore, to describe the association between physical activity and the metabolic syndrome and to test whether fitness level modifies this relationship.

RESEARCH DESIGN AND METHODS — Physical activity was measured objectively using individually calibrated heart rate against energy expenditure. $V\text{O}_{2max}$ was predicted from a submaximal exercise stress test. Fat mass and fat-free mass (FFM) were calculated using impedance biometry. A metabolic syndrome score was computed by summing the standardized values for obesity, hypertension, hyperglycemia, insulin resistance, hypertriglyceridemia, and the inverse level of HDL cholesterol and was expressed as a continuously distributed outcome. To correct for exposure measurement error, a random subsample (22% of cohort) re-attended for three repeat measurements in the year following the first assessment.

RESULTS — The relationship of $V\text{O}_{2max}$ (ml $O_2 \cdot kg_{FFM}^{-1} \cdot min^{-1}$) and the metabolic syndrome score was of borderline significance after adjusting for age, sex, physical activity, and measurement error ($\beta = -0.58$, $P = 0.06$). The magnitude of the association between physical activity ($kJ \cdot d^{-1} \cdot kg_{FFM}^{-1}$) and the metabolic syndrome was more than three times greater than for $V\text{O}_{2max}$ (standardized $\beta = -1.83$, $P = 0.0042$). $V\text{O}_{2max}$, however, modified the relationship between physical activity energy expenditure and metabolic syndrome ($P = 0.036$).

CONCLUSIONS — This study demonstrates a strong inverse association between physical activity and metabolic syndrome, an association that is much steeper in unfit individuals. Thus, prevention of metabolic disease may be most effective in the subset of unfit inactive people.

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Over the course of the past half century, metabolic disease has emerged as the most prevalent cause of death in industrialized nations (1). It is likely that during this time there has been a secular decline in the amount of physical activity energy expenditure (PAEE) (2), which may have resulted in lower cardiorespiratory fitness. These ecologic data suggest that physical inactivity may be one of the main modifiable risk factors in the etiology of the common complex metabolic disorders (3). Physical activity is inherently difficult to measure precisely. Thus, analytical epidemiologic studies (cross-sectional and cohort) have primarily demonstrated the association between cardiorespiratory fitness and metabolic risk or the association with self-reported participation in recreational activities and metabolic risk (4–9). The dearth of data derived from directly assessed physical activity means that the etiologic role of physical activity is unclear. Resolving the relative importance of fitness and activity requires an understanding of the degree of measurement error in the two exposures. Determining the independent effect of PAEE on metabolic risk is important because it may be more feasible to encourage populations to make small changes in energy expenditure rather than trying to improve fitness level. It is also uncertain whether the effects of physical activity are the same in hereditarily fit individuals (i.e., those who, even when physically inactive, maintain high levels of cardiorespiratory fitness) and unfit individuals. If there were evidence of effect modification, this would give rise to possibilities for targeted prevention.

Although specific metabolic phenotypes are important to consider when assessing the role of physical activity in disease, the clustering of these phenotypes may also be important (10,11). The metabolic syndrome, which is a cluster of metabolic abnormalities that predisposes the individual to high risk of early mortality (12), is one way of summarizing overall risk. Although several studies have attempted to explore the relationship between subjectively determined physical activity and metabolic syndrome (4–8), all have used a categorical definition of metabolic syndrome, which limits the power to detect an association. The use of a categorical definition of metabolic syndrome and the combination of weak measurements of physical activity, most often through questionnaire (13), and more precise measurements of fitness, usually using an exercise stress test, means that false-negative associations for physical activity with the metabolic syndrome are more likely to be observed than for fitness (14,15).

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Abbreviations: FFM, fat-free mass; PAEE, physical activity energy expenditure.

In the present study, we explore the independent associations between PAEE and cardiorespiratory fitness, after correction for bivariate measurement error, with a continuously distributed and standardized summary score for metabolic syndrome. This study was conducted in a large nondiabetic Caucasian population from the U.K., in which repeat objective measures of PAEE and cardiorespiratory fitness are available.

RESEARCH DESIGN AND METHODS

A total of 874 healthy Caucasian participants took part in the study. Complete clinical, anthropometric, energy expenditure, and cardiorespiratory fitness data were available for all participants. The volunteers were all participants in the Medical Research Council (MRC) Ely Study (16,17), a prospective population-based cohort study of the etiology and pathogenesis of type 2 diabetes and related metabolic disorders. Ethical permission for the study was granted by the Cambridge local research ethics committee.

Repeated-measures substudy

During the year following the first assessment, a random subsample of 193 individuals from the main cohort (22%) reattended our laboratories 3, 6, and 9 months after their first visit for the reassessment of cardiorespiratory fitness, PAEE, and resting energy expenditure. The characteristics of the subsample and the methods used at re-attendance, which did not differ from the main study, have been described in detail previously (18).

Anthropometric and metabolic tests

Participants attended the laboratory after a 10-h overnight fast. After collection of standard anthropometric data by trained observers with participants wearing indoor clothing, all participants provided written informed consent. Height and weight were measured using a rigid stadiometer and calibrated scales. Body circumference was measured in duplicate using a metal tape. Quantities of fat mass and fat-free mass (FFM) were calculated using a standard impedance technique (Bodystat, Isle of Man, U.K.). Blood pressure was measured in a seated position using an Accutorr automatic sphygmomanometer (Datascope, Cambridge, U.K.). Systolic and diastolic blood pressures were measured in triplicate at minute intervals, and the mean of the three measurements was used in analyses. Participants then received an explanation of the procedure for the collection of blood. A sample of fasting blood was taken, and participants drank 75 g of anhydrous glucose (BMS Laboratories, Beverley, U.K.) dissolved in 250 ml of water over the course of between 2 and 5 min. Additional blood samples were then taken at 30 and 120 min. Blood samples were immediately placed on ice and centrifuged on site. Plasma samples were aliquoted, packed in ice, and transferred to the laboratory, where they were stored at −70°C within 4 h. Plasma glucose was measured in the routine NHS laboratory at Addenbrooke's Hospital using the hexokinase method, and triglycerides and HDL cholesterol were measured using the RA 1000 (Bayer Diagnostics, Basingstoke, U.K.) with a standard enzymatic method. Plasma specific insulin was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels. Cross-reactivity was <0.2% with intact proinsulin at 400 pmol/l and <1% with 32-33 split proinsulin at 400 pmol/l. Interassay coefficients of variation (CVs) were 6.6% at 28.6 pmol/l (n = 99), 4.8% at 153.1 pmol/l (n = 102), and 6.0% at 436.7 pmol/l (n = 99), respectively.

Assessment of resting and exercise oxygen consumption–heart rate relationship

The method for individually calibrating heart rate against energy expenditure has been described in detail elsewhere (19,20). However, in summary, the oxygen consumption–heart rate relationship was assessed at rest with the participant lying and then seated, using an oxygen analyzer calibrated daily with 100% nitrogen and fresh air as standard gases (PK Morgan, Kent, U.K.). Participants bicycled on a cycle ergometer at several different workloads to provide the slope and the intercept of the line relating energy expenditure to heart rate. Each subject cycled at 50 revolutions per minute and the workload was progressively increased from 0 W through 37.5, 75, and 125 W in 5-min stages. At each workload, three separate readings of heart rate, minute volume, and expired air oxygen concentration were recorded. Energy expenditure (kJ/min) was calculated at each time point as oxygen consumption (ml/min) × 20.35 (21). Mean resting energy expenditure was taken as the average of the lying and sitting values. The slope and intercept of the least-squares regression line of the exercise points were calculated. Flex heart rate, which is the point used to discriminate between rest (below flex) and exercise (above flex), was calculated as the mean of the highest resting pulse rate and the lowest on exercise. Exercising energy expenditure was predicted from the slope and intercept of the regression line calculated during the exercise test. Participants wore heart rate monitors (Polar Electro, Kemple, Finland) continuously during the waking hours over the following 4 days. Sleeping energy expenditure was calculated as 95% of basal metabolic rate; this was derived from published prediction equations (22,23). PAEE was calculated by subtracting mean resting energy expenditure from total energy expenditure, expressed per unit FFM, and was computed for each day and averaged over the 4-day period.

Assessment of cardiorespiratory fitness

Cardiorespiratory fitness ($V_{O_{2max.pred}}$) was predicted as oxygen uptake at maximal heart rate (220 minus age) determined from the regression line established during the individual calibration for the relationship between oxygen consumption and heart rate. $V_{O_{2max.pred}}$ is expressed per unit FFM (24).

Statistical analyses

All insulin and glucose data were logarithmically transformed owing to their nonnormal distribution (geometric means and 95% CIs are presented in the results). All data were analyzed in their continuous form.

Calculation of the metabolic syndrome *z* score

A summary variable for the metabolic syndrome was computed based broadly on World Health Organization criteria (12). This variable was derived by standardizing and then summing the following continuously distributed indexes of obesity (BMI + waist-to-hip ratio/2), hypertension (systolic blood pressure + diastolic blood pressure/2), insulin resistance (fasting insulin), hyperglycemia (2-h plasma glucose), inverted fasting HDL cholesterol, and hypertriglyceridemia to create a z score. The standardizing of these factors was achieved by subtract-

Table 1—*Descriptive characteristics of participants*

	Men	Women
n	378	490
Age (years)	54.0 ± 11.1	53.3 ± 10.4
Height (cm)	175.1 ± 6.4	162.2 ± 6.3‡
Weight (kg)	82.2 ± 12.3	68.8 ± 13.2‡
Fat mass (kg)	20.1 ± 7.0	25.9 ± 9.1‡
FFM (kg)	62.1 ± 7.5	42.9 ± 6.0‡
$V\text{O}_{2\text{max.pred}}$ (l O_2/min)	2.7 ± 0.7	1.8 ± 0.7‡
Total energy expenditure (MJ/d)	14.3 ± 3.0	10.3 ± 2.1‡
Resting energy expenditure (MJ/d)	9.6 ± 1.8	7.3 ± 1.3‡
Physical activity energy expenditure (MJ/d)	4.7 ± 2.6	3.0 ± 1.8‡
BMI (kg/m^2)	26.8 ± 3.6	26.1 ± 4.8*
Waist-to-hip ratio	0.95 ± 0.07	0.79 ± 0.07†
Systolic blood pressure (mmHg)	129 ± 15	122 ± 15†
Diastolic blood pressure (mmHg)	79.1 ± 10.6	76.4 ± 9.4†
Triglycerides (mmol/l)	1.44 ± 0.63	1.23 ± 0.64†
HDL cholesterol (mmol/l)	1.33 ± 0.36	1.64 ± 0.41†
Fasting insulin (pmol/l)	42.52 (42.46–42.59)	37.78 (37.73–37.83)
2-h glucose (mmol/l)	5.42 (5.39–5.45)	5.39 (5.35–5.40)

Data are means ± SD or geometric means (95% CI). One-way ANOVA for differences between sexes: *$P <$ 0.05; †$P < 0.001$; ‡$P < 0.0001$.

ing the sample mean from the individual mean and then dividing by the SD (of the sample mean). The mean of this continuously distributed metabolic syndrome score is therefore zero by definition. In parallel, we also calculated a metabolic syndrome score without the obesity components.

Linear regression models

Simple and multiple linear regressions were performed using SAS (Windows version 8; SAS Institute, Cary, NC) and the regression coefficients for the exposure variables were presented. The univariate correction was undertaken using the reliability coefficient (25). The multivariate correction factors for PAEE and $V\text{O}_{2\text{max.pred}}$ were estimated using the method described by Wong et al. (15).

Using multiple linear regression modeling, the independent associations of PAEE per unit FFM and $V\text{O}_{2\text{max.pred}}$ per unit FFM with metabolic syndrome were assessed. These analyses were adjusted for sex and age. Further generalized linear modeling analyses were then undertaken to test the interaction between PAEE per unit FFM and $V\text{O}_{2\text{max.pred}}$ per unit FFM on metabolic syndrome. In all analyses, PAEE and $V\text{O}_{2\text{max.pred}}$ were entered as continuous variables and corrected for error using the method described below. The β-coefficients are standardized to the variance in the exposure variable and can be interpreted as how much of a unit change in the outcome is associated with a 1-SD change in the exposure.

Statistical correction for measurement error

The within-individual and between-individual mean squares and the reliability coefficients for PAEE and $V\text{O}_{2\text{max.pred}}$ were estimated using the formulae described by Armstrong et al. (25). We subsequently applied these error coefficients to the linear regression models constructed to test the association of PAEE and $V\text{O}_{2\text{max.pred}}$ with the metabolic syndrome. The purpose of applying these error coefficients was to control statistically for measurement bias that occurs when comparing exposures that are measured with a varying degree of precision. Error correction coefficients were calculated under the assumption that the errors associated with repeated measures for the same individual were independent. We have previously demonstrated the utility of the method described by Armstrong et al. (25) in models designed to test the relative associations of physical activity and cardiorespiratory fitness with other metabolic phenotypes (14,15,18,25).

RESULTS — The descriptive characteristics of participants are shown in Table 1. Men were significantly taller and heavier and had higher FFM ($P < 0.001$). Fat mass was significantly higher in women ($P < 0.001$). Significant sex differences were also observed for resting energy expenditure, total energy expenditure, and PAEE ($P < 0.001$). Adjusting PAEE for FFM did not fully remove the sex difference (76 ± 42 vs. 70 ± 40 kJ/kg_{FFM}; $P < 0.05$). Cardiorespiratory fitness ($V\text{O}_{2\text{max.pred}}$) was significantly higher in men when expressed in absolute terms ($P < 0.001$) and when adjusting $V\text{O}_{2\text{max.pred}}$ for differences in FFM (43.4 ± 9.7 vs. 41.5 ± 12.8 ml $O_2 \cdot kg_{FFM}^{-1} \cdot min^{-1}$; $P < 0.05$).

In Table 1, the eight variables comprising the metabolic syndrome risk score are shown. BMI ($P < 0.05$), waist-to-hip ratio, systolic and diastolic blood pressures, triglycerides, and fasting insulin ($P < 0.001$) were significantly higher in men, whereas HDL cholesterol was significantly higher in women ($P < 0.001$).

Using error correction coefficients derived from the repeated-measures substudy, we were able to adjust the standardized regression coefficients for $V\text{O}_{2\text{max.pred}}$ ($ml\,O_2 \cdot kg_{FFM}^{-1} \cdot min^{-1}$) and PAEE (kJ/$kg_{FFM}$) for confounders (age and sex) and for measurement error. $V\text{O}_{2\text{max.pred}}$ ($ml\,O_2 \cdot kg_{FFM}^{-1} \cdot min^{-1}$) was significantly related to the metabolic syndrome score after adjusting for age, sex, and PAEE ($P = 0.03$). After bivariate error correction, the association between fitness and metabolic syndrome was reduced to a level of borderline significance ($P = 0.06$). The association between PAEE (kJ/kg_{FFM}) and the metabolic syndrome score was more than three times stronger than the associations for $V\text{O}_{2\text{max.pred}}$. PAEE was significant in models adjusted for age, sex, and $V\text{O}_{2\text{max.pred}}$ ($P < 0.0001$) and after adjustment for age, sex, $V\text{O}_{2\text{max.pred}}$, and bivariate measurement error ($P = 0.0042$). An interaction was also observed between $V\text{O}_{2\text{max.pred}}$ and PAEE on the metabolic syndrome after adjustment for age and sex ($P = 0.001$) and after adjustment for age, sex, and bivariate error correction ($P = 0.036$). In the model for the revised metabolic syndrome score, which excluded the obesity component, we also assessed the interaction between PAEE and $V\text{O}_{2\text{max.pred.}}$ In this model, $V\text{O}_{2\text{max.pred}}$, PAEE, and the interaction ($V\text{O}_{2\text{max.pred}}$*PAEE) were significant after adjustment for age and sex: $\beta = -0.086$, $P = 0.013$; $\beta = -0.267$, $P <$

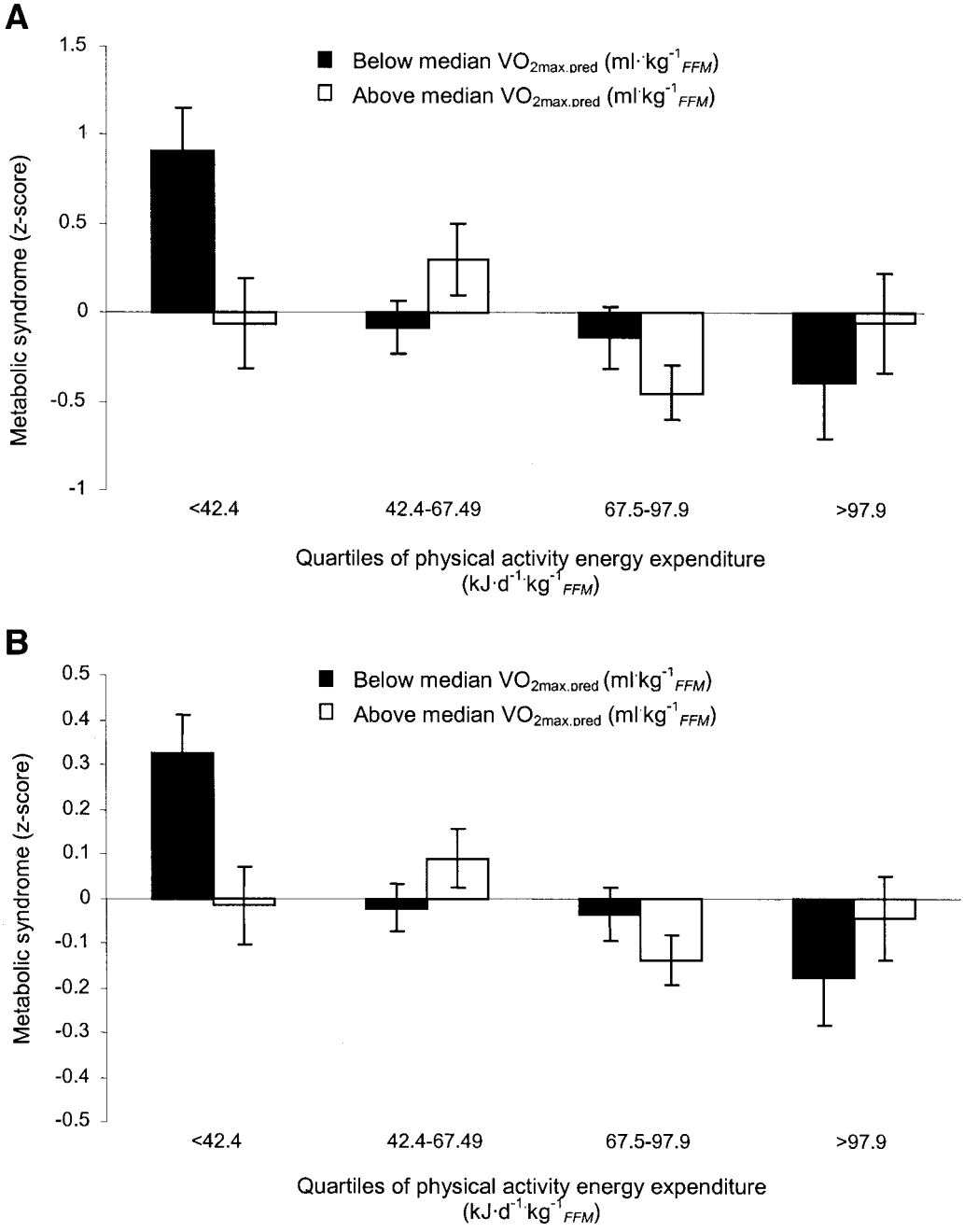

Figure 1—A: *The interaction of PAEE and cardiorespiratory fitness on the metabolic syndrome in a population-based sample of healthy middle-aged men and women from the U.K.* (n = 874) *after adjustment for bivariate measurement error, age, and sex* (P *for interaction = 0.036). Median* $VO_{2max.pred}$ *is sex specific.* B: *The interaction of PAEE and cardiorespiratory fitness on the metabolic syndrome (excluding obesity) in a population-based sample of healthy middle-aged men and women from the U.K.* (n = 874) *after adjustment for bivariate measurement error, age, and sex* (P *for interaction = 0.016). Median* $VO_{2max.pred}$ *is sex specific.*

0.0001; and $\beta = 0.042$, $P = 0.003$, respectively. These associations persisted after bivariate error correction: $\beta = -0.235$, $P = 0.029$; $\beta = -0.716$, $P = 0.0012$; and $\beta = 0.140$, $P = 0.016$, respectively.

The interaction between PAEE and cardiorespiratory fitness ($VO_{2max.pred}$) is shown in Fig. 1*A*. Data are stratified above and below the median for cardiorespiratory fitness and by quartile of PAEE. In Fig. 1*B*, the same interaction is displayed, excluding the obesity component from the metabolic syndrome score to demonstrate the obesity-independent relationships. Both figures indicate that those who are below the median in cardiorespiratory fitness benefit most from being physically active in relation to the metabolic syndrome. However, the inclusion of obesity in the metabolic syndrome score results in a markedly higher mean level of metabolic syndrome in "low-fitness" inactive individuals (z score = 0.89) by comparison with the model in which obesity is removed from the outcome (z score = 0.32).

CONCLUSIONS — The present study reports observations on the individual and combined importance of PAEE and cardiorespiratory fitness ($VO_{2max.pred}$) in the etiology of the metabolic syndrome. After adjusting for the effects of measurement error, we observed a strong and significant inverse association between PAEE and metabolic syndrome. The association between $VO_{2max.pred}$ and the met-

abolic syndrome is substantially weaker than that for PAEE and is not significant. However, $V\text{O}_{2\text{max.pred}}$ modified the association between PAEE and the metabolic syndrome, such that although in unfit people PAEE was strongly inversely related with the metabolic syndrome, in fit people, no such relationship exists. It is likely that by adjusting $V\text{O}_{2\text{max.pred}}$ for PAEE, the hereditary components of fitness are revealed. Therefore, individuals with a high $V\text{O}_{2\text{max.pred}}$ after adjustment for PAEE are most probably those with a hereditary predisposition to a high oxidative capacity.

Understanding the relative importance of cardiorespiratory fitness and physical activity in the etiology of the metabolic syndrome is important for the translation of epidemiologic findings into preventive action. Cardiorespiratory fitness as assessed through a maximal oxygen consumption test is complex, because it is influenced by modifiable factors, such as volume, intensity, and mode of activity (26) and cardiovascular pathology (27), as well as nonmodifiable factors, such as genotype (28,29) and early life development (8,30). In an early study reported by Bouchard et al. (31), substantial between-individual variance in adaptation to exercise was observed. Subsequent studies have reported inheritance of fitness phenotypes (32) and linkage between genomic regions and fitness phenotypes (33). In combination, these data provide compelling evidence that improvements in fitness may be more easily achieved in certain individuals than in others and that this difference relates to genetic or other nonmodifiable factors.

The different relationships that fitness and physical activity have with the metabolic syndrome observed here and elsewhere emphasize the importance of considering the generalizability of activity and fitness data from populations that differ in these characteristics (34–36). Several studies have reported that fitness is a strong independent risk factor for several metabolic morbidities (37–40) and all-cause early mortality (41,42), which is not surprising, because fitness is also an outcome of physical activity (31,43), which is believed to be cardioprotective. However, because cardiorespiratory fitness is a function of both physical activity and nonmodifiable factors, without knowledge of activity level, it is impossible to determine the extent to which fitness can be changed or how these changes will correspond with improvements in health.

Unraveling the separate effects of fitness and PAEE is difficult and is largely dependent on the precision with which exposure and outcome are measured. The present study was undertaken in a large randomly selected population-based cohort in which objective assessments of energy expenditure measured by individually calibrated heart rate monitoring was available. $V\text{O}_{2\text{max.pred}}$ was derived from submaximally measured oxygen uptake during an exercise stress test. Our measure of PAEE correlates highly against doubly labeled water (44) and is considerably more reliable and valid than subjective approaches (45). Our submaximal measure of fitness is less precise than a true maximal test but was selected because it is feasible in a population sample (46). Nonetheless, our measure of fitness is likely to be of greater precision than other fitness tests that do not involve direct assessment of oxygen uptake (26). Furthermore, use of repeated measurements for $V\text{O}_{2\text{max.pred}}$ and PAEE, and the subsequent correction of measurement error, results in increased and more comparable precision of our exposures (15,47). This is in contrast to other studies that have attempted to address the association between physical activity, fitness, and metabolic disease in population-based cohorts (4–8).

To adjust for between-individual variation in $V\text{O}_{2\text{max.pred}}$ and PAEE, these measures were normalized by FFM. Normalizing $V\text{O}_{2\text{max}}$ by FFM is a preferred approach, by comparison to normalization by body weight (i.e., $V\text{O}_{2\text{max}}$/kg) (24). PAEE, however, is dependent on body size (48), and body mass may be the most appropriate variable by which to adjust PAEE. However, because body mass is one of the components in the calculation of BMI and BMI was used as a subcomponent (weighted at 1/12) in the calculation of the metabolic syndrome score, we normalized PAEE by FFM and analyzed our data with and without the obesity component in the outcome. The purpose of this was to demonstrate that obesity, which is part of the exposure and outcome in the initial model, does not explain our findings. Thus, it seems unlikely that our findings are attributable to chance, measurement error, or other known forms of bias.

In our study, as with most cross-sectional data, it is not possible to fully determine direction of causality. This is because although physical inactivity and low cardiovascular fitness may cause metabolic morbidity, metabolic morbidity is also likely to result in decreased physical activity and fitness. Participants in the present study were free from diabetes according to World Health Organization criteria at initial enrollment into the study. Furthermore, individuals were screened immediately before the exercise stress test for abnormal cardiac function via physician-surveyed electrocardiography. These exclusion criteria indicate that the existence of cardiovascular pathology is likely to be rare in this cohort. Because the relationship between workload and oxygen consumption may differ in people with peripheral and pulmonary vascular disease by comparison with healthy individuals (27), the extrapolation of findings from the present study to populations in which cardiovascular pathology is common should be done with caution.

Our data indicate that energy expended solely through physical activity equating to ~1.8 and 2.6 MJ/d for women and men, respectively (i.e., the equivalent of moving from the lowest to the second quartile of PAEE in Fig. 1*A*), may be sufficient to significantly decrease risk of metabolic syndrome. In unfit people, a change in activity level of this magnitude could theoretically correspond to a maximally decreased BMI of ~4 kg/m^2, a maximally decreased diastolic blood pressure of ~10 mmHg, or a maximally increased HDL cholesterol of ~1.5 mmol/l, for example, or the combination of a fraction of the value for each trait. This could be achieved through walking, household tasks, and other activities, which need not be fitness enhancing. The modes of physical activity that are common at population level are primarily nonstructured forms, and although structured exercise training is an important way in which metabolic syndrome may be prevented, our data indicate that elevated energy expenditure through less defined modes of physical activity is likely to be important in the primary prevention of metabolic disease. Increasing those forms of activity may be easier to achieve at population level than increasing structured exercise training.

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