Physical Activity Energy Expenditure Predicts Progression Toward the Metabolic Syndrome Independently of Aerobic Fitness in Middle-Aged Healthy Caucasians

The Medical Research Council Ely Study

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OBJECTIVE — To examine over a period of 5.6 years the prospective associations between physical activity energy expenditure (PAEE), aerobic fitness ($V\text{O}_{2max}$), obesity, and the progression toward the metabolic syndrome in a population-based cohort of middle-aged men and women ($n = 605$) who were free of the metabolic syndrome at baseline.

RESEARCH DESIGN AND METHODS — PAEE was measured objectively by 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 were assessed by bio-impedance. 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 expressed as a continuously distributed outcome. Generalized linear models were used to examine the independent prospective associations between PAEE and $V\text{O}_{2max}$ and the metabolic syndrome score after adjusting for sex, baseline age, smoking, socioeconomic status, follow-up time, and baseline phenotypes.

RESULTS — PAEE predicted progression toward the metabolic syndrome, independent of baseline metabolic syndrome, body fat, $V\text{O}_{2max}$, and other confounding factors (standardized $\beta = -0.00085$, $P = 0.046$). This association was stronger when excluding the adiposity component from the metabolic syndrome (standardized $\beta = -0.0011$, $P = 0.035$). $V\text{O}_{2max}$ was not an independent predictor of the metabolic syndrome after adjusting for physical activity (standardized $\beta = 0.00011$, $P = 0.93$).

CONCLUSIONS — PAEE predicts progression toward the metabolic syndrome independent of aerobic fitness, obesity, and other confounding factors. This finding underscores the importance of physical activity for metabolic disease prevention even when an improvement in aerobic fitness is absent.

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Abbreviations: FFM, fat-free mass; PAEE, physical activity energy expenditure; SES, socioeconomic status; WHR, waist-to-hip ratio.

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

The metabolic syndrome is loosely defined as a cluster of cardiovascular risk factors, including disturbed insulin and glucose metabolism, hypertension, overweight and abdominal obesity, and dyslipidemia (elevated triglycerides and decreased HDL cholesterol levels). Furthermore, this syndrome predicts the development of type 2 diabetes, cardiovascular disease, and all-cause mortality in nondiabetic subjects (1,2).

Previous cross-sectional (3–6) and prospective (7,8) studies suggest that aerobic fitness and physical activity protect against the development of the metabolic syndrome. However, free-living physical activity (i.e., body movement) and physical activity energy expenditure (PAEE) are inherently difficult to measure precisely, and previous epidemiological studies have primarily relied on self-reported physical activity when examining associations with the metabolic syndrome (3–5,7,8). We recently reported a strong inverse cross-sectional association between objectively measured PAEE and a continuously distributed summary score for the metabolic syndrome (6), an association that was independent of aerobic fitness. We also demonstrated a similar association in a population-based sample of 9- to 10-year-old children (9). However, it is unknown whether the association of objectively measured physical activity and the metabolic syndrome, independent of aerobic fitness, is also observed in prospective data.

The aim of the present study, therefore, was to determine whether PAEE predicts progression toward the metabolic syndrome in a randomly selected population-based sample of middle-aged Cauca-

sian men and women who were free of the metabolic syndrome at baseline.

RESEARCH DESIGN AND METHODS

— Participants were selected from the Medical Research Council (MRC) Ely Study (10), a prospective population-based cohort study of the etiology and pathogenesis of type 2 diabetes and related metabolic disorders. The volunteers were originally recruited in 1990–1992. The objective measures of physical activity and aerobic fitness were taken in 1994–1996 at the first follow-up, which constitutes the baseline for these analyses. At baseline, socioeconomic status (SES) was collected by self-report. Our measure of SES was based on job title, formal qualifications for the job, and the specific type of work performed. Participants were restudied in 2001–2003 (follow-up), representing a median ± SD follow-up period of 5.6 ± 0.30 years. Complete data on biochemical and anthropometric variables from baseline and follow-up and baseline PAEE were available in 689 subjects. Of these, 84 subjects (46 male) were classified as having the metabolic syndrome at baseline according to World Health Organization criteria (11) and were excluded from the present analyses. Thus, the present report includes 605 (249 male) healthy middle-aged adults. All participants provided written informed consent. Ethical permission for the study was granted by the Cambridge Local Research Ethics Committee.

Anthropometric and metabolic tests

The procedure for data collection was the same at baseline and follow-up. Participants attended the laboratory after an overnight fast. Height and weight were measured using a rigid stadiometer and calibrated scales in light clothing. Body circumference was measured in duplicate using a metal tape. Resistance (**Ω**) was assessed using a standard bioimpedance technique (Bodystat, Isle of Man, U.K.). This method has previously been shown to be valid (12) and reliable (13). Total body water and fat-free mass (FFM) were calculated using the impedance index (height^2/resistance) and body weight and resistance according to published equations (14). Fat mass was calculated as body weight minus FFM. Percentage of body fat was calculated as fat mass/body weight × 100.

Blood pressure was measured in the 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 these 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 anhydrous glucose (BMS Laboratories, Beverley, U.K.) dissolved in 250 ml of water over the course of 2–5 min. Further blood samples were then taken at 30 and 120 min. Blood samples were centrifuged and aliquoted on site and immediately placed on ice. Plasma samples were aliquoted, packed in ice, and transferred to the laboratory where they were stored at −70°C within 4 h. Blood samples were measured in the routine National Health Service laboratory at Addenbrooke's Hospital in Cambridge. Plasma glucose was measured using the hexokinase method, and plasma triglycerides and HDL cholesterol were measured with standard enzymatic methods. 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 baseline PAEE and aerobic fitness

PAEE was measured using the flex heart rate method. This method has been described in detail elsewhere (6,10). The energy expenditure (i.e., oxygen consumption)/heart rate relationship was assessed supine and sitting at rest, using an oxygen analyzer calibrated daily with 100% nitrogen and fresh air as standard gases (PK Morgan, Kent, U.K.). Participants then bicycled on a cycle ergometer at different workloads (0–125 W in 5-min stages of 25-W increments) to provide the slope and the intercept of the line relating energy expenditure to heart rate. Flex heart rate was calculated as the mean of the highest resting heart rate and the lowest heart rate while exercising. This point was used in the analysis of free-living minute-by-minute heart rate data to discriminate between rest and exercise. Below the flex heart rate point, energy expenditure was assumed to be equivalent to resting energy expenditure. Energy expenditure above the flex point was predicted from the individual heart rate/energy expenditure regression line. Participants wore heart rate monitors (Polar Electro, Kemple, Finland) continuously during the waking hours over the following 4 days. PAEE (kilojoules per day) was calculated by subtracting resting energy expenditure from the estimated total energy expenditure and thereafter averaged over the 4-day period and expressed in relation to FFM per day (kJ · FFM^{-1} · day^{-1}).

Aerobic fitness ($V_{O_{2max}}$) was predicted as oxygen uptake at maximal heart rate (220 − age) by extrapolation of the regression line established during the individual calibration for the relationship between oxygen consumption and heart rate. $V_{O_{2max}}$ is expressed per unit of FFM (6).

The metabolic syndrome

Broadly based on the definition proposed by the World Health Organization (11), we constructed a standardized continuously distributed variable (*zMS*) for the metabolic syndrome, which we have described in detail previously (6,9). This variable was derived by standardizing and then summing the following continuously distributed indexes of obesity (BMI + WHR/2), where WHR is waist-to-hip ratio; hypertension (systolic blood pressure + diastolic blood pressure/2); hyperglycemia (2-h plasma glucose); insulin resistance (fasting insulin); inverted fasting HDL cholesterol; and hypertriglyceridemia to create a *Z* score. This composite score is referred to as *zMS*. We also calculated a metabolic syndrome score without the adiposity component (BMI + WHR). This score is referred to as *zMS-Ob*. Baseline and follow-up *Z* scores were computed with the same transformation, i.e., the mean and SD of baseline values. The purpose of using a continuously distributed variable was to maximize statistical power (15).

Statistical analyses

Descriptive summary statistics were calculated using means and SDs at baseline and follow-up. Fasting insulin and 2-h glucose were logarithmically transformed (ln) owing to their skewed distribution

Table 1—*Anthropometric and metabolic characteristics of participants at baseline and follow-up, the MRC Ely study 1994–2003*

	Men (n = 246)		Women (n = 359)	
	Baseline	Follow-up	Baseline	Follow-up
Age (years)	53.3 ± 10.5	58.9 ± 10.6*	53.1 ± 10.1	58.7 ± 10.2*
Height (cm)	175.3 ± 6.8	175.0 ± 6.7	162.3 ± 6.1†	162.0 ± 6.2†
Weight (kg)	80.6 ± 10.6	81.2 ± 12.2‡	68.0 ± 12.6	69.5 ± 14.7*
BMI (kg/m^2)	26.2 ± 2.9	26.5 ± 3.5†§	25.8 ± 4.4	26.4 ± 6.2*†
WHR	0.94 ± 0.06	0.94 ± 0.07	0.79 ± 0.06	0.81 ± 0.07*†
Body fat (%)	23.0 ± 4.3	25.0 ± 4.6*	36.5 ± 6.2	38.8 ± 6.7*†
DBP (mmHg)	76.9 ± 9.8	79.8 ± 10.0*	73.3 ± 9.0	75.9 ± 9.4*†
SBP (mmHg)	125.8 ± 13.1	130.8 ± 14.1*	121.9 ± 14.2	126.9 ± 15.6*†
Triglycerides (mmol/l)	1.32 ± 0.55	1.37 ± 0.70	1.13 ± 0.49	1.23 ± 0.63*†
HDL (mmol/l)	1.37 ± 0.35	1.34 ± 0.33‡	1.66 ± 0.41	1.62 ± 0.41†§
Fasting insulin (mmol/l)	37.0 (34.5–39.7)	47.9 (44.6–51.3)*	35.4 (33.4–37.5)	42.9 (40.5–45.4)*
2-h glucose (mmol/l)	5.0 (4.8–5.2)	5.6 (5.3–5.8)*	5.2 (5.0–5.4)	5.6 (5.4–5.8)*
PAEE (kJ · FFM^{-1} · day^{-1})	80.1 ± 43.5		70.1 ± 43.60†	
$V_{O_{2MAX}}$ (ml · FFM^{-1} · min^{-1})	44.1 ± 9.2		42.0 ± 13.4#	

Data are means ± SE and geometric mean (95% CI). *$P < 0.001$, ‡$P < 0.05$, and §$P < 0.01$ for baseline vs. follow-up. †$P < 0.001$, #$P < 0.05$ for women vs. men. DBP, diastolic blood pressure; SBP, systolic blood pressure.

(geometric mean and reference intervals [1.96 × SD] are presented in RESULTS).

To examine whether PAEE and aerobic fitness independently predicted the subcomponents of the metabolic syndrome, we first modeled the association between PAEE and aerobic fitness and the different subphenotypes of the metabolic syndrome score at follow-up (i.e., BMI, WHR, systolic and diastolic blood pressure, triglycerides, HDL cholesterol, 2-h glucose, and insulin). These analyses were undertaken in generalized linear models adjusted for age, sex, smoking, SES, respective baseline subphenotype, and duration of follow-up. Where obesity was not the outcome of interest, we assessed whether baseline PAEE and aerobic fitness was associated with a change in each phenotype per se and whether PAEE and aerobic fitness predicted these phenotypes after adjustment for baseline percentage body fat. We then tested whether PAEE and aerobic fitness predicted *zMS* in two models. The first model (obesity dependent) included all subcomponents of the metabolic syndrome and was adjusted for baseline *zMS*, sex, age, smoking, SES, and follow-up time. In the second model (obesity independent), the adiposity component was excluded from the outcome, and adjustments were made for baseline *zMS-Ob* (without the adiposity component), sex, age, smoking, SES, follow-up time, and baseline fat mass (%). Since aerobic fitness has been shown to modify the cross-sectional association between PAEE and the metabolic syndrome (6), the interaction term PAEE × aerobic fitness was introduced to test whether aerobic fitness modified the prospective associations between PAEE and the subphenotypes and summary score of metabolic syndrome at follow-up. All data were analyzed in their continuous form, although data are stratified by quartiles of PAEE for illustrative purposes. All analyses were conducted using SPSS for Windows (version 11; SPSS, Chicago, IL). $P < 0.05$ denotes statistical significance.

RESULTS — Table 1 shows the anthropometric and metabolic characteristics of participants at baseline and follow-up stratified by sex within the population free from metabolic syndrome at baseline. Body weight, BMI, WHR, percentage body fat, systolic and diastolic blood pressure, HDL cholesterol, fasting insulin, and 2-h glucose all significantly increased over the 5.6-year follow-up period in both men and women ($P < 0.05$). Plasma triglyceride concentration significantly increased only in women ($P < 0.001$). PAEE ($P < 0.001$) and aerobic fitness ($P < 0.05$) was significantly higher in men than in women at baseline. Between baseline and follow-up there were 64 (10.6%) incident cases (18.9 cases per

Table 2 —*Independent associations of baseline PAEE (kJ · FFM^{-1} · day^{-1}) with fasting insulin, the subcomponents, and the summary variable, with* (zMS) *and without* (zMS-Ob) *the adiposity component of the metabolic syndrome 5.6 years later*

Outcome (SD)	PAEE β-coefficients (95% CI)
Insulin	−0.002 (−0.0037 to −0.00053)*
BMI	0.00004 (−0.00076 to 0.00084)
WHR	0.00058 (−0.0006 to 0.0017)
2-h glucose	−0.00008 (−0.0016 to 0.0015)
DBP	−0.00086 (−0.0024 to 0.0007)
SBP	−0.002 (−0.0037 to −0.00064)*
Triglycerides	0.000088 (−0.0015 to 0.0015)
HDL	0.00074 (−0.0005 to 0.002)
zMS	−0.00085 (−0.00177 to −0.000068)†
zMS-Ob	−0.0011 (−0.0021 to −0.0006974)‡

Outcomes were expressed as standardized *Z* scores for analysis (n = 605). Data are are adjusted for age, sex, smoking, SES, aerobic fitness, and baseline phenotype. All variables except BMI and WHR are additionally adjusted for baseline percentage of body fat. *$P < 0.01$, †$P < 0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure.

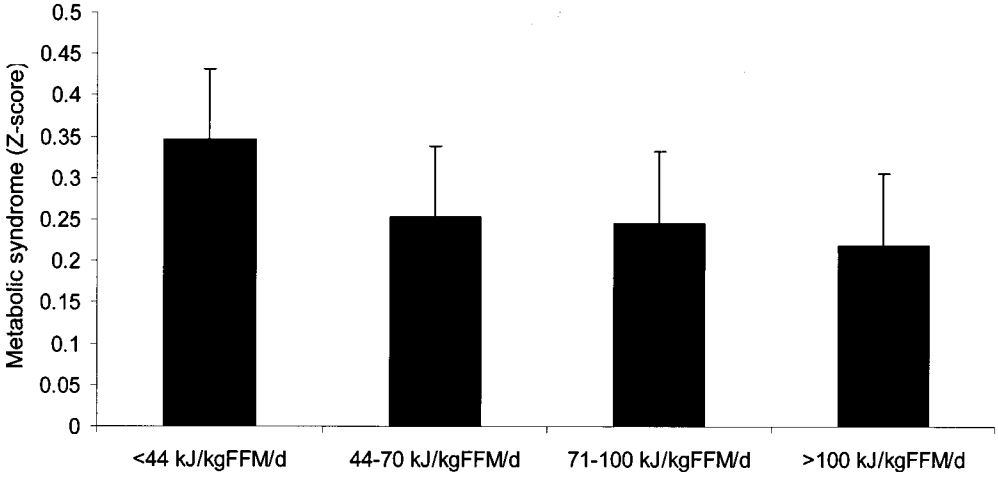

Figure 1—*Adjusted means (95% CI) of metabolic syndrome (zMS) at follow-up by quartiles of PAEE ($kJ \cdot FFM^{-1} \cdot day^{-1}$) over a period of 5.6 years in middle-aged men and women (n = 605) who were healthy at baseline. Data are adjusted for sex, age, smoking, SES, aerobic fitness, baseline metabolic syndrome, and follow-up time. Post hoc analyses revealed a significant difference between the first and second quartile (P = 0.044).*

1,000 person-years of follow-up) of metabolic syndrome (38 men).

Table 2 shows the prospective associations between baseline PAEE and the subcomponents of the metabolic syndrome, expressed standardized to the SD of each of the predictor and outcome variables. Since all of the outcomes in Table 2 are expressed in the same unit (SD), it is possible to directly compare the association of PAEE with each of these outcomes. Baseline PAEE significantly predicted fasting insulin at follow-up after adjustment for baseline age, sex, smoking, SES, fasting insulin, aerobic fitness, and duration of follow-up (standardized $\beta = -0.0012$, $P = 0.01$). This association was not affected by further adjustment for baseline BMI (standardized $\beta = -0.0013$, $P = 0.005$), baseline WHR (standardized $\beta = -0.0012$, $P = 0.007$), or baseline percentage body fat (standardized $\beta = -0.0012$, $P = 0.006$). Baseline PAEE also significantly predicted systolic blood pressure at follow-up independently of the potential confounders listed above (standardized $\beta = -0.0022$, $P = 0.005$). Aerobic fitness was not significantly associated with any of the subcomponents of the metabolic syndrome, and no significant interactions between PAEE and aerobic fitness were observed.

Baseline PAEE significantly predicted progression toward the metabolic syndrome at follow-up (standardized $\beta = -0.00085$ $P = 0.046$), independently of aerobic fitness and other potential confounding factors. We thereafter reanalyzed our data expressing $V_{O_{2max}}$ and PAEE in relation to body weight, and our results remained essentially unchanged. PAEE ($kJ \cdot kg^{-1} \cdot d^{-1}$) was borderline significantly (standardized $\beta = -0.0012$, $P = 0.059$) associated with the metabolic syndrome score independent of aerobic fitness ($ml \cdot kg^{-1} \cdot min^{-1}$) (standardized $\beta = -0.0022$, $P = 0.30$). Substituting percentage body fat for BMI as the indicator of overall obesity when calculating the metabolic syndrome score did not materially change our findings.

In Fig. 1, the prospective associations between quartiles of baseline PAEE and the metabolic syndrome score at follow-up is shown. Post hoc analyses revealed a significant difference between the first and second quartile of PAEE in levels of metabolic syndrome ($P = 0.044$).

We examined the association between baseline PAEE and the metabolic syndrome score excluding the adiposity component from the outcome and adjusting for baseline obesity. Again, a significant inverse association was found, and further adjustment for baseline obesity did not significantly alter this association (standardized $\beta = -0.0011$, $P = 0.035$). Likewise, adjustment for baseline percentage body fat (or change in percentage of body fat) as the obesity indicator did not change the association (standardized $\beta = -0.0012$, $P = 0.035$). Finally, we reanalyzed our data, excluding the adiposity component and adjusting for baseline obesity, expressing $V_{O_{2max}}$ and PAEE in relation to body weight. Again, PAEE was significantly associated with the metabolic syndrome score (standardized $\beta = -0.0015$, $P = 0.023$) independent of aerobic fitness (standardized $\beta = 0.00056$, $P = 0.83$) and other potential confounding factors.

We also examined whether aerobic fitness modified the association between PAEE and the metabolic syndrome, with and without the adiposity component. No significant interactions between PAEE and aerobic fitness were observed for any of these models ($P > 0.4$).

Finally, we reanalyzed all our data excluding participants who reported medical treatment either at baseline or at follow-up ($n = 127$) to account for potential effect modification by this factor. There was no evidence that treatment with medications altered the association between PAEE and the development of the metabolic syndrome.

CONCLUSIONS — In this study, we have described the prospective association over a 5.6-year period between objectively measured PAEE and aerobic fitness with the metabolic syndrome in a population-based sample of middle-aged men and women who were free of the metabolic syndrome at baseline. Our results suggest that PAEE predicts progression toward the metabolic syndrome in a dose-dependent manner and that this association is not explained by obesity, level of aerobic fitness, or other potential confounding factors.

This is the first prospective population-based study to use valid and objective methods to describe the association between PAEE and the metabolic syndrome. Previous prospective studies using self-reported physical activity have produced conflicting results. For example, although Laaksonen et al. (8) reported an inverse relationship between leisure-time physical activity and the development of the metabolic syndrome in middle-aged men, Palaniappan et al. (16) found no relationship in the multiethnic

Atherosclerosis Risk in Communities (ARIC) study. Our data provide support for the role of physical activity in the prevention of the metabolic syndrome. In contrast to previous prospective studies that did not adjust the effects of fitness for physical activity (8), we did not observe an association between aerobic fitness and the metabolic syndrome after adjusting for physical activity level. This difference may be due to a lower degree of measurement error for the physical activity variable used in the present study and to different analytical procedures. Laaksonen et al. (8) assessed physical activity by self-report and reported on the associations between time spent in moderate and vigorous intensity of physical activity, whereas our measure of physical activity is based on the amount of energy expenditure above resting levels, which takes into account all types and intensities of activity performed in daily life and not only structured exercise and related activities. Furthermore, the prospective relationship observed between activity and the metabolic syndrome was independent of aerobic fitness in the present study, whereas Laaksonen et al. (8) modeled the associations of fitness and reported physical activity in separate analyses.

We observed a statistically significant, linear dose-response association between PAEE and the metabolic syndrome. Although our participants progressed toward a worsening of the metabolic syndrome during the follow-up period, our stratified analyses (Fig. 1) indicated a significant difference in metabolic syndrome score at follow-up between the first and second quartile of PAEE. Our study was not powered to explore the possibility of nonlinearity; thus, studies that seek to determine whether there is an important threshold are required. Energy expenditure through physical activity equating to ~1.7 MJ/day would be necessary to move from the first to the second quartile of PAEE. This amount of physical activity is approximately equal to 1 h of brisk walking. This amount of activity could be achieved through all types of activities that increase energy expenditure above rest, which need not be fitness enhancing. Although structured exercise is important in the prevention of the metabolic syndrome, our data suggest that everyday activities, which elevate PAEE, are likely to be important in the primary prevention of the metabolic syndrome, whatever the level of aerobic fitness. Moreover, our observation of a dose-response association was similar when excluding the adiposity component from the metabolic syndrome, indicating that the prospective effects of physical activity are not entirely mediated by changes in adiposity.

We have recently reported that aerobic fitness modifies the association between PAEE and the metabolic syndrome in cross-sectional analyses in the same cohort (6) and in children (9). We were not able to replicate these findings in the present prospective analyses. This may then mean that PAEE is equally important in relation to the metabolic syndrome regardless of initial fitness level over time. From a public health perspective, the presence of a fitness-independent association between PAEE and the metabolic syndrome is important because it may be more feasible to encourage populations to make small changes in physical activity level, rather than to increase aerobic fitness.

The ability to detect the association between PAEE and change in metabolic components that we report in the present study is dependent upon several factors. These include the precision of exposure and outcome measurement, the sample size, and the magnitude of the association between exposure and outcome. The present study was undertaken in a large randomly selected population-based cohort, in which objective assessments of energy expenditure is available. PAEE was assessed through individually calibrated heart rate against resting and exercising energy expenditure. Our measure of PAEE compares well against doubly labeled water-measured PAEE (17,18), which by many is considered the gold-standard method for assessing free-living energy expenditure. Moreover, the flex heart rate method is considerably more reliable and valid than subjective techniques such as questionnaire and interview (19). To adjust for between-individual variation in PAEE, we normalized PAEE by FFM. This has been suggested as an appropriate approach when normalizing PAEE data (20). However, as in all observational studies, our data are only suggestive of a causal effect of PAEE.

Our measure of aerobic fitness is less precise than a true maximal test but was selected because it is feasible in a population-based study (21). It is unlikely, however, that predicted $V\mathrm{O}_{2max}$ from our submaximal test would bias our results, as the error in predicting maximal heart rate is likely to be random across the population. We have previously reported the reliability coefficient and the inter- and intra-individual covariances in a repeated-measures substudy, indicating that our submaximal test is reliable over time (22).

We used epidemiological methods of assessing obesity in this study. Thus, it is possible that residual potential confounding by obesity may persist. The situation is made more complicated because some authorities consider obesity as a risk factor for the metabolic syndrome, whereas others consider it to be part of the syndrome itself and thus include it as a part of the definition. However, our results were similar when we excluded obesity from the outcome and adjusted for it as an exposure. Moreover, the results were unchanged when using waist circumference or percentage of body fat, the latter obtained by bio-impedance, which is likely to be more precise than BMI.

In summary, our data suggest that physical activity is an important etiological factor in the development of the metabolic syndrome. These effects are not explained by obesity and are independent of aerobic fitness and other known potential confounding factors. The major implication of this study is that efforts to prevent the metabolic syndrome should focus on increasing PAEE.

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