Increase in Physical Activity Energy Expenditure Is Associated With Reduced Metabolic Risk Independent of Change in Fatness and Fitness

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OBJECTIVE — We sought to examine whether change in physical activity energy expenditure (PAEE) is associated with change in metabolic risk factors and whether this association is independent of change in fat mass and aerobic fitness.

RESEARCH DESIGN AND METHODS — In a population-based sample of 176 men and 217 women followed prospectively for 5.6 years, we measured PAEE by individually calibrated heart rate monitoring, aerobic fitness, total body fat (fat mass), and metabolic risk factors (blood pressure, fasting triglycerides, HDL cholesterol, insulin, and 2-h glucose) at baseline and follow-up.

RESULTS — A 100 J · kg fat-free mass $(FFM)^{-1}$ · min^{-1} increase in PAEE from baseline to follow-up reduced triglycerides by 3.5% (95% CI 0.03–5.7) in men and 3.2% (0.02–5.4) in women, fasting insulin by 5.3% (1.0–7.5) in men and women, and 2-h glucose by 3.2% (0.3–5.3) in men and 3.1% (0.3–5.2) in women, after adjustment for sex, age, smoking status, aerobic fitness, baseline phenotype, and change in fat mass. In general, the magnitudes of association for change in fat mass with metabolic risk factors were two to three times stronger than for PAEE.

CONCLUSIONS — Increasing levels of physical activity may protect against metabolic disease even in the absence of improved aerobic fitness and reduced body fatness. Therefore, the combination of increasing levels of physical activity and avoidance of gain in fat mass is likely to be the most successful approach for preventing cardiovascular and metabolic disease.

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Low levels of habitual physical activity, poor aerobic fitness, and obesity have been associated with an increased risk of type 2 diabetes (1–9). To an extent, the elevated risk of type 2 diabetes associated with physical inactivity and obesity is mediated by other risk factors such as glucose intolerance and insulin resistance (10–17). Thus, although low levels of physical activity, poor aerobic fitness, and overweight are strong predictors of type 2 diabetes and metabolic risk, the independent contribution of these factors is not firmly established (18–21).

Recently, Christou et al. (20) concluded that body fatness is a better predictor of cardiovascular and metabolic risk factors than aerobic fitness and that level of body fatness is associated with an adverse risk profile independent of aerobic fitness. By contrast, Lee et al. (21) concluded that for a given level of abdominal obesity, men with higher levels of aerobic fitness had substantially lower metabolic risk compared with men with lower fitness levels. Furthermore, previous studies assessing physical activity by self-report indicate that visceral fat is associated with metabolic risk independent of physical activity, whereas physical activity is not associated with metabolic risk factors after adjusting for visceral fat (22,23).

We have shown that objectively assessed physical activity energy expenditure (PAEE) is associated with clustered metabolic risk (24) and predicts progression toward the metabolic syndrome in a dose-response manner, independent of levels of obesity or aerobic fitness (25). However, we have not previously assessed whether change in PAEE is associated with individual metabolic risk factors or whether this association is independent of change in aerobic fitness and body fatness.

In the present study, we examined whether associations between change in PAEE and metabolic risk factors and clustered metabolic risk are independent of change in aerobic fitness and adiposity in a population-based prospective cohort study of middle-aged men and women.

RESEARCH DESIGN AND METHODS

— Participants were selected from the Medical Research Council Ely Study (24,25), a prospective population-based cohort study of the etiology and pathogenesis of type 2 diabetes and related metabolic disorders. The volunteers were examined between 1994 and 1996 (baseline) and again between 2001 and 2003 (follow-up). The median follow-up duration was 5.6 years. A cohort of 739 (311 male and 428 female) subjects provided complete data on anthropometric and body composition variables and physical activity energy expenditure data at baseline. Of these, 240 volunteers were aged >65 years at follow-up and were excluded for safety reasons from undertaking the exercise test. Thus, no measure of fitness or PAEE was available in these individuals at follow-up. Of the remaining 499 individuals, 48 were treated with antihypertensive medication equiva-

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

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

lent to 50 mg Atenolol at follow-up and were also excluded from the exercise test. PAEE was successfully assessed at baseline and follow-up in 393 (87% of those eligible) volunteers (176 male and 217 female) and constitutes the sample for this report. After adjustment for age, no significant difference was observed in sex distribution; anthropometric, cardiovascular, or metabolic characteristics; or aerobic fitness levels of those included in the present report by comparison with those who are not. All participants provided written informed consent, and ethical permission for the study was granted by the Cambridge Local Research Ethics Committee.

Our measures of anthropometry and body composition have previously been described (24,25). Systolic and diastolic blood pressures were measured in the seated position using an Accutorr automatic sphygmomanometer (Datascope, Cambridge, U.K.). A sample of fasting blood was taken, and participants drank 75 g anhydrous glucose (BMS Laboratories, Beverley, U.K.) dissolved in 250 ml water. Further blood samples were taken at 120 min. Plasma and serum were extracted immediately, aliquoted, packed in ice, and transferred to the laboratory where they were stored at −70°C within 4 h. Blood samples were analyzed at the NHS laboratory at Addenbrooke's Hospital in Cambridge, U.K. Plasma glucose was measured using the hexokinase method, and plasma triglycerides, cholesterol, LDL cholesterol, 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 and interassay coefficients of variation have been reported elsewhere (24).

Assessment of physical activity energy expenditure and aerobic fitness

At both baseline and follow-up, resting energy expenditure was measured by indirect calorimetry in the fasted state, after ~10 min of supine rest. At baseline, the energy expenditure/heart rate relationship was assessed during a graded exercise test on a cycle ergometer using indirect calorimetry (PK Morgan oxygen analyzer) (24,25). At follow-up, volunteers were individually calibrated for the relationship between energy expenditure and heart rate during a submaximal walking treadmill test. Oxygen uptake and CO_2 production were continuously measured by indirect calorimetry throughout the test (Vista XT metabolic system; Vacumed, Ventura, CA). Expired air was measured with a turbine flowmeter, carbon dioxide concentration ($FECO_2$) with an infrared sensor, and oxygen concentration (FEO_2) with a fast differential paramagnetic sensor. Gas analyzers were calibrated with gases of known composition, and the turbine flowmeter was calibrated with a 3-l syringe before each measurement.

At both baseline and follow-up and for each individual, the slope and intercept of the least-squares regression line of the energy expenditure and heart rate relationship were calculated. Flex heart rate was calculated as the mean of the highest resting heart rate and the lowest heart rate while exercising. Participants wore heart rate monitors (Polar Electro, Kemple, Finland) continuously during the waking hours during the 4 days from which minute-by-minute energy expenditure was calculated and averaged. PAEE (kJ/min) was calculated by subtracting resting energy expenditure from total energy expenditure. Aerobic fitness ($V_{O_{2max}}$) was estimated as V_{O_2} at the age-predicted maximal heart rate by extrapolation of the regression line established during the individual calibration for the relationship between oxygen consumption and heart rate. To adjust for between-individual differences in body size, PAEE and $V_{O_{2max}}$ are expressed per unit of FFM (26).

Statistical methods

All metabolic risk factors at baseline and follow-up (i.e., systolic and diastolic blood pressures, HDL cholesterol, triglycerides, 2-h glucose, and insulin) were standardized by calculating *Z* scores, based on the baseline distribution, separately for men and women. We also constructed a standardized continuously distributed variable for clustered metabolic risk, which we have previously described in detail (24,25). This variable was derived by standardizing and then summing the following continuously distributed indexes to create a *Z* score: hypertension ([systolic blood pressure + diastolic blood pressure]/2), 2-h plasma glucose, fasting insulin, inverted fasting HDL cholesterol, and triglycerides.

Descriptive characteristics are summarized as means ± SD at baseline and follow-up. Fasting insulin, 2-h glucose, and triglycerides were logarithmically transformed owing to their skewed distributions (geometric means [95% CIs] are presented in RESULTS). Associations between variables were examined using Pearson correlation coefficients and partial correlation coefficients.

To examine whether change in PAEE and change in fat mass (both changes were from baseline to follow-up) were independently associated with individual risk factors and with clustered metabolic risk, we fitted multiple linear regression models with each risk factor in turn as the outcome and with change in PAEE and in fat mass as exposures. In the models, we also adjusted for age, sex, smoking status, aerobic fitness, and duration of follow-up.

To examine whether the associations between change in PAEE and fat mass and the outcome variables were independent of baseline levels of PAEE and fat mass, we also fit models including all the exposures and potential confounders listed above, as well as baseline PAEE and terms representing the interactions between change in PAEE and baseline PAEE and change in fat mass and baseline fat mass.

RESULTS — Descriptive characteristics of the participants are shown in Table 1. Significant differences between men and women were observed for all variables at baseline and follow-up except for age (all $P < 0.01$). Body weight, fat mass, waist circumference, systolic and diastolic blood pressures, 2-h glucose, fasting insulin, PAEE, and $V_{O_{2max}}$ increased significantly, and FFM decreased significantly in both sexes between baseline and follow-up (all $P < 0.001$). Fasting HDL cholesterol decreased significantly in women ($P < 0.001$) but not in men. Fasting triglycerides increased in women ($P < 0.001$) and did not change in men. The prevalences of overweight and obesity were 43.1 and 14.5%, respectively, in our cohort.

Change in PAEE was not significantly associated with change in fat mass ($r = 0.02$, $P = 0.65$) or change in waist circumference ($r = 0.01$, $P = 0.97$) but was weakly correlated with change in aerobic fitness ($r = 0.18$, $P < 0.001$).

Table 2 shows the independent associations between change in PAEE and each individual metabolic risk factor at follow-up and between change in fat mass and each individual metabolic risk factor at follow-up. Change in PAEE was significantly and inversely associated with 2-h glucose, fasting insulin, triglycerides, and clustered metabolic risk. After translating

Table 1—*Descriptive characteristics of participants (n = 393) at baseline and follow-up: the Medical Research Council Ely Study, 1994–2003*

	Men (n = 176)		Women (n = 217)	
Variable	Baseline	Follow-up	Baseline	Follow-up
Age (years)	49.7 ± 8.0	55.3 ± 8.2*	49.2 ± 7.4	54.8 ± 7.5*
Weight (kg)	82.5 ± 10.5	83.6 ± 11.8†	69.0 ± 12.6	70.7 ± 15.0†‡
Height (cm)	175.7 ± 6.2	175.5 ± 6.1	163.2 ± 6.0	163.1 ± 6.0‡
Fat mass (kg)	18.9 ± 5.4	21.3 ± 6.3*	24.8 ± 8.5	27.0 ± 10.3*‡
FFM (kg)	63.6 ± 6.7	62.4 ± 7.3*	44.2 ± 5.4	43.6 ± 6.0*‡
Waist (cm)	94.1 ± 8.6	97.9 ± 9.0*	79.4 ± 10.1	84.7 ± 12.0*‡
Diastolic BP (mmHg)	79.0 ± 10.6	82.0 ± 10.9*	73.0 ± 10.3	76.0 ± 9.0*‡
Systolic BP (mmHg)	128.5 ± 14.4	132.9 ± 15.0*	119.6 ± 13.3	124.7 ± 13.5*‡
2-h glucose (mmol/l)¶	5.1 (4.9–5.3)	6.0 (5.7–6.3)*	5.1 (4.9–5.3)	5.7 (5.5–6.0)*‡
Insulin (mU/l)¶	41.1 (37.8–44.7)	51.4 (46.7–56.6)*	35.7 (33.0–38.5)	40.9 (37.7–44.8)*‡
Triglycerides (mmol/l)¶	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.0 (1.0–1.1)	1.1 (1.0–1.2)*‡
HDL cholesterol (mmol/l)	1.33 ± 0.35	1.31 ± 0.33	1.66 ± 0.43	1.61 ± 0.40*‡
$V_{O_{2MAX}}$ (ml · kg FFM^{-1} · min^{-1})	46.8 ± 10.8	57.9 ± 14.1*	43.7 ± 11.9	55.4 ± 14.2*‡
PAEE (kJ · kg FFM^{-1} · min^{-1})	0.12 ± 0.05	0.16 ± 0.07*	0.11 ± 0.05	0.14 ± 0.07*‡

Data are means ± SD or geometric means (95% CI) unless otherwise indicated. No significant time-by-sex interactions were observed. *$P < 0.001$ and †$P < 0.01$, ANOVA for between-time differences; ‡$P < 0.001$, ANOVA for between-sex differences. BP, blood pressure.

the regression coefficients in Table 2 (which represent changes in Z scores of log-transformed values) back to the original scale for the outcomes, a 100 J · kg FFM^{-1} · min^{-1} increase in PAEE from baseline to follow-up corresponded with a reduction in 2-h glucose of 3.2% (95% CI 0.33–5.3) in men and 3.1% (0.33–5.2) in women. For the same unit change in PAEE, fasting insulin was reduced by 5.3% (1.00–7.5) in both men and women, and fasting trigylcerides were reduced by 3.5% (0.3–5.7) in men and 3.2% (0.2–5.4) in women. There was also a 0.92 SD (0.38–1.47) reduction in clustered metabolic risk. Change in fat mass was significantly and positively associated with diastolic blood pressure, systolic blood pressure, 2-h glucose, fasting insulin, triglycerides, and clustered metabolic risk. For every 1 kg increase in fat mass from baseline to follow-up, there was an associated 0.04 SD (0.02–0.04) increase in clustered metabolic risk.

We next examined whether the associations between change in PAEE and metabolic risk factors were independent of baseline levels of activity by fitting the term representing the interaction between change in PAEE and baseline PAEE into the model. Including baseline PAEE into the model did not change the magnitude or directions of associations with 2-h glucose, fasting insulin, and triglycerides (data not shown), and no significant interaction was observed ($P = 0.84$), indicating that the association between change in PAEE and metabolic risk factors was independent of baseline levels of activity. Similarly, no significant interaction was observed between change in fat mass with baseline fat mass ($P = 0.43$). No significant interaction ($P = 0.2$) was observed between change in PAEE and change in fat mass in any of our analyses, indicating separate and independent effects of physical activity and adiposity on metabolic risk factors.

Because visceral adiposity is an important etiological factor for several of the metabolic traits examined, we also assessed the role of waist circumference as a mediating factor. The results from the models where waist circumference was included did not differ from those in which fat mass was included. Increase in waist circumference was significantly associated with the same individual risk factors as when fat mass was modeled as the exposure (data not shown).

The magnitude of the associations with change in PAEE and with change in fat mass for each of the risk factors was compared by including these variables as standardized Z scores from the baseline distribution. Similar to our original

Table 2—*Independent associations between change in PAEE and individual metabolic risk factors and clustered metabolic risk 5.6 years later, as well as between change in fat mass and individual metabolic risk factors and clustered metabolic risk 5.6 years later*

Outcome	Change in PAEE	P	Change in FM	P
Diastolic BP (mmHg)	−0.88 (−1.79 to 0.04)	0.06	0.04 (0.03 to 0.06)	<0.0001
Systolic BP (mmHg)	−0.68 (−1.62 to 0.27)	0.16	0.04 (0.02 to 0.06)	<0.0001
2-h glucose (mmol/l)	−1.40 (−2.70 to −0.10)	0.035	0.03 (0.008 to 0.05)	0.008
Insulin (mU/l)	−1.32 (−2.46 to −0.18)	0.023	0.06 (0.04 to 0.08)	<0.0001
Triglycerides (mmol/l)	−0.88 (−1.76 to −0.003)	0.049	0.03 (0.02 to 0.05)	<0.0001
HDL cholesterol (mmol/l)	0.21 (−0.56 to 0.98)	0.60	−0.01 (−0.02 to 0.003)	0.14
Clustered metabolic risk	−0.92 (−1.47 to −0.38)	0.001	0.04 (0.03 to 0.04)	<0.0001

Data are regression coefficients (95% CI), which represent the expected change in the outcome (expressed as a standardized Z score) for a 1-unit increase in either change in PAEE or change in fat mass (FM); $n = 393$. Fasting insulin, triglycerides, and 2-h glucose are log transformed. Data are adjusted for age, sex, smoking status, aerobic fitness, baseline phenotype, and duration of follow-up. Change in PAEE and change in fat mass are included in the same model. BP, blood pressure.

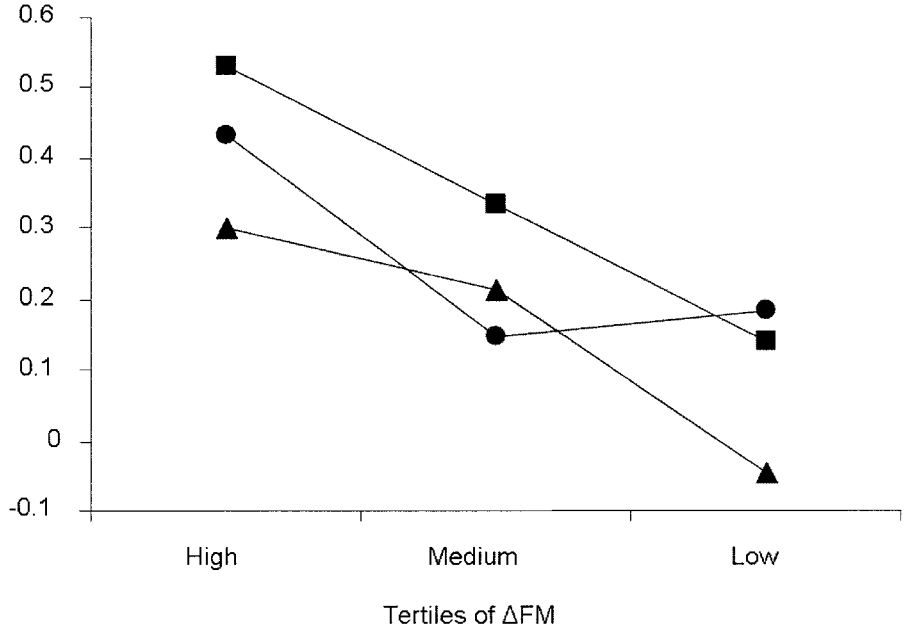

Figure 1—*Clustered metabolic risk (Z score) at follow-up in middle-aged white men and women (n = 393) stratified by tertiles of change in fat mass (ΔFM) and physical activity (■, top tertile of PAEE; ●, middle tertile of PAEE; ▲, lowest tertile of PAEE). Data are adjusted for sex, age, change in aerobic fitness, smoking, baseline metabolic risk score, and follow-up time (P = 0.001 in continuous analysis).*

model, change in PAEE was significantly and inversely associated with fasting insulin, triglycerides, and 2-h glucose ($P < 0.03$), independent of change in fat mass and the same confounding factors as above. However, the magnitudes were generally two to three times greater for change in fat mass compared with change in PAEE (coefficients ranged from 0.12 to 0.19 for fat mass vs. −0.02 to −0.09 for PAEE).

We also attempted to account for residual confounding by obesity by reanalyzing our data having normalized PAEE to body weight (instead of FFM), by expressing PAEE in absolute values, and by introducing body weight as a covariate. However, this did not influence any of the associations. Change in aerobic fitness was not significantly associated with any of the metabolic risk factors in any of the models after statistically controlling for PAEE and fat mass.

We then excluded all individuals with diagnosed diabetes and impaired glucose tolerance ($n = 23$) at baseline and reanalyzed our data. The associations between change in PAEE and fasting insulin and change in PAEE and triglycerides were the same, whereas a 1 kJ · kg FFM^{-1} · min^{-1} increase in PAEE during follow-up was associated with a modest improvement in 2-h glucose (a reduction of 1.64 SD [95% CI 0.42–2.84], $P = 0.012$). The associations between changes in fat mass were unchanged after exclusion of individuals with impaired glucose tolerance and type 2 diabetes at baseline (data not shown).

Figure 1 shows the association between change in PAEE and fat mass, stratified by tertiles, with clustered metabolic risk at follow-up after adjustment for sex, age, aerobic fitness, smoking, baseline phenotype, and follow-up time. Increasing levels of PAEE were associated with favorable metabolic risk scores across tertiles of fat mass.

CONCLUSIONS — Increase in physical activity over a period of 5.6 years was associated with improvements in insulin sensitivity, glucose tolerance, fasting triglycerides, and clustered metabolic risk in a population of middle-aged white men and women. Furthermore, these associations are independent of changes in adiposity, aerobic fitness, and the baseline activity levels.

Our results support previous findings, which indicate that moderate- and vigorous-intensity exercise is beneficial for insulin sensitivity and glycemic control in healthy individuals and that the beneficial effect of activity is independent of weight change (11–17). For example, results from a recent exercise training study suggest that exercise duration is more strongly associated with improvements in insulin action than with exercise intensity (13). Studies elsewhere have shown that moderate (14,15) and vigorous (16,17) exercise result in improvements in glucose homeostasis, even in the absence of marked weight loss. However, none of these studies assessed whether the beneficial effects of physical activity on insulin sensitivity and glucose metabolism are independent of improvements in aerobic fitness.

The response of blood lipids to exercise training has mainly been attributable to weight loss or improvements in aerobic fitness (28). For example, Hunter and colleagues (22,23) did not observe any association between physical activity and metabolic risk factors after controlling for obesity in healthy men and women. Change in intra-abdominal adipose tissue was suggested as the mechanism linking physical activity with these risk factors. A possible explanation for the different conclusions drawn in that study and ours may relate to the degree of measurement error for the physical activity variable; Hunter and colleagues (22,23) assessed physical activity by self-report and expressed it as an activity index on a scale from 1 to 5. This method is less precise than objective measurements of PAEE, and measurement error associated with subjective physical activity assessment increases with body weight (29). By contrast, a recent randomized control trial in overweight men and women with mild-to-moderate dyslipidemia showed that the total volume, but not intensity, of exercise improved lipidemia. The authors suggested that these effects were independent of weight loss and enhancements in aerobic fitness (30). Although we found evidence that change in physical activity was associated with triglyceride levels, we did not observe any associations between change in PAEE and total cholesterol, LDL cholesterol, or HDL cholesterol, indicating that the beneficial effects of physical activity on these risk factors may be less apparent than for other traits.

We observed strong and statistically significant associations between change in measures of obesity (i.e., fat mass and waist circumference) and multiple metabolic risk factors after adjustment for change in PAEE and aerobic fitness. This suggests that increased body fat mass is associated with changes in metabolic risk factors independent of changes in physical activity level and aerobic fitness. Our results also suggest that body fat mass is a stronger predictor of multiple risk factors

than are PAEE and aerobic fitness. Consistent with our observations, a recent cross-sectional study in healthy men concluded that higher fat mass was associated with an adverse risk profile, independent of aerobic fitness (20). However, we did not observe a significant association between aerobic fitness and any metabolic risk factor after controlling for PAEE and body fat mass in the present study. The results presented here therefore extend previous cross-sectional findings by showing that changes in both PAEE and body fatness are independently associated with multiple metabolic risk factors. Furthermore, the effects of physical activity on some of the metabolic risk factors appear to be direct and not mediated by body fatness.

The effect sizes of our observations are small; i.e., an increase in PAEE by 150 kcal per day (equivalent to 30 min of brisk walking) was associated with a reduction of about 1–2% in insulin resistance, glucose intolerance, and fasting triglycerides in our sample. However, the finding that increased physical activity is inversely associated with metabolic risk factors independent of changes in aerobic fitness, body fatness, or baseline activity levels has several important implications. First, increased levels of physical activity are associated with considerable improvements in cardiovascular and metabolic risk factors, regardless of fitness level and degree of adiposity. These benefits are also independent of an individual's initial activity level, suggesting that changing activity patterns in late middle-age is beneficial for cardiovascular health. From a public health perspective, an association between change in PAEE and metabolic risk factors independent of aerobic fitness is important because it may be feasible to encourage populations to make small improvements in their overall levels of physical activity, which may not necessarily result in improved fitness. Second, although body fatness was a stronger predictor of these risk factors than habitual physical activity, increasing levels of activity may confer health benefits even if fat mass is unchanged. Third, the strong and independent associations between indicators of obesity with metabolic risk factors reinforce the message that prevention of unhealthy weight gain and excess body fat is an important goal to reduce metabolic risk.

Because the present study is observational, the extent to which causality can be inferred is less than that when considering data from appropriately designed clinical trials. However, statistical models, such as those reported on here, where change in the independent variables is modeled against change in the dependent variable, may be less prone to confounding than conventional association models, thus strengthening the evidence of causality (31). This is because persistence in confounding in a change model requires that the confounder(s) change in a way similar to the exposure over time. Furthermore, our observations are supported by extensive and compelling experimental data in animals (32–36) and clinical trial data in humans (37,38) that demonstrate that exercise training and lifestyle modification confer positive effects on a wide variety of metabolic traits.

An additional possible limitation of our study is that the individual calibration procedures for energy expenditure at baseline and follow-up differed. Indeed, PAEE increased between baseline and follow-up, which may reflect a change in procedure. However, all participants were individually calibrated for the relationship between energy expenditure and heart rate at baseline and follow-up exams. Thus, because the exposure is characterized as the difference in PAEE from baseline to follow-up, it is unlikely that a change in procedure would introduce bias, as all individuals would be affected proportionately.

At both time points, aerobic fitness was estimated from a graded submaximal exercise test. Our submaximal measure of fitness is less precise than a true maximal test but was selected for its feasibility in a population sample of older individuals (39). 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 (40). More important, it is unlikely that predicted fitness 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 intra- and interindividual covariances in a repeated-measures substudy, indicating that our submaximal test is reliable over time (41). Similar to PAEE, it is unlikely that the change in protocol between exams biased our results, as the error would be similar for all individuals. To exclude this possibility, we expressed our exposure variables as standardized *Z* scores from the baseline distribution and reanalyzed our data; the associations and their statistical significance were unchanged (data not shown).

We conclude that change in physical activity level is inversely associated with insulin resistance, glucose intolerance, and hyperlipidemia, independent of change in body fatness, aerobic fitness, and initial levels of activity. This may have implications for metabolic risk reduction, as increasing levels of physical activity may have protective effects without improvements in aerobic fitness or reduced body fat mass irrespective of the initial levels of activity. However, body fatness was more strongly related to multiple metabolic risk factors and clustered metabolic risk than to physical activity after partitioning out the effect of change in activity and fitness. Therefore, the combination of increasing levels of physical activity and avoidance of unhealthy weight gain is likely to be the most successful approach for the prevention of metabolic disease.

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