Increase in physical activity energy expenditure is associated with reduced metabolic risk independent of change in fatness and fitness

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Abstract

**Objective:** 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 (5.6 years), we measured PAEE by individually calibrated heart rate monitoring, aerobic fitness, total body fat (FM), and metabolic risk factors (blood pressure, fasting triglycerides, HDL-cholesterol, insulin and 2-hour glucose) at baseline and follow-up.

**Results:** A 100 J/kgFFM/min increase in PAEE from baseline to follow-up reduced triglycerides by 3.5% (95% CI 0.03% to 5.7%) in men and 3.2% (95% CI 0.02% to 5.4%) in women, fasting insulin [reduced by 5.3% (95% CI 1.0% to 7.5%) in men and women], and 2 hour glucose [reduced by 3.2% (95% CI 0.3% to 5.3%) in men and 3.1% (0.3% to 5.2%) in women] at follow-up, 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 2 to 3 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.
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 independently 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 than men with lower fitness levels. Furthermore, previous studies assessing physical activity by self-report indicate that visceral fat is associated with metabolic risk independently 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 towards the metabolic syndrome in a dose-response manner, independently 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 and 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**

**Study population**
Participants were selected from the Medical Research Council (MRC) Ely Study (24, 25), a prospective population-based cohort study of the aetiology 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 males and 428 females) provided complete data on anthropometric and body composition variables, and physical activity energy expenditure data at baseline. Of these, 240 volunteers were older than 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 anti-hypertensive medication equivalent 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 males and 217 females) and constitutes the sample for this report. After adjustment for age, no significant difference was observed in gender-distribution, the 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.
Measurements

Our measures of anthropometry and body composition have been described previously (24, 25).

Systolic and diastolic blood pressure was measured in the seated position using an Accutorr automatic sphygmomanometer (Datascope, Cambridge, UK). A sample of fasting blood was taken, and participants drank 75 g anhydrous glucose (BMS Laboratories, Beverley, UK) dissolved in 250 ml of water. Further blood samples were taken at 120-mins. Plasma and serum were extracted immediately, aliquoted, packed in ice, and transferred to the laboratory where they were stored at -70°C within 4hrs. Blood samples were analyzed at the NHS laboratory at Addenbrooke's Hospital in Cambridge. Plasma glucose was measured using the hexokinase method and plasma triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured with standard enzymatic methods. Plasma specific insulin was determined by two-site immunometric assays with either 125I or alkaline phosphatase labels. Cross-reactivity and inter-assay coefficient 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 (REE) was measured by indirect calorimetry in the fasted state, after approximately 10 minutes of supine rest. At baseline, the energy expenditure (EE) - heart rate (HR) relationship was assessed during a graded exercise test on a cycle ergometer and using indirect calorimetry (PK Morgan oxygen analyzer, Kent, UK) (24, 25).

At follow-up volunteers were individually calibrated for the relationship between EE and heart rate during a sub-maximal walking treadmill test. Oxygen uptake and CO₂ production were continuously measured by indirect calorimetry throughout the test (Vista XT metabolic system; Vacumed Inc., Ventura, CA). Expired air was measured with a turbine flowmeter, carbon dioxide concentration (FECO₂) with an infrared sensor, and oxygen concentration (FEO₂) with a fast differential paramagnetic sensor. Gas analysers were calibrated with gases of known composition and the turbine flow meter was calibrated with a 3-litre 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 EE and heart rate relationship were calculated. Flex HR was calculated as the mean of the highest resting HR and the lowest HR while exercising. Participants wore HR monitors (Polar Electro Ltd, Kemple, Finland) continuously during the waking hours during the 4-days from which minute-by-minute EE was calculated and averaged over the time the monitor was worn. PAEE (kJ min⁻¹) was calculated by subtracting REE from TEE. Aerobic fitness (VO₂ max) was estimated as VO₂ at 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 VO₂ max are expressed per unit of fat-free mass (26).

Statistical Methods

All metabolic risk factors at baseline and follow-up (i.e. systolic and diastolic blood pressure, HDL cholesterol, triglycerides, 2-hour glucose, and insulin) were standardised 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 (zMS), which we have described in detail previously (24, 25). This
variable was derived by standardizing and then summing the following continuously distributed indices; hypertension ([SBP + DBP] / 2], fasting plasma glucose, fasting insulin, inverted fasting HDL-C, and triglycerides to create a z-score.

Descriptive characteristics are summarised as means and standard deviations (SD) at baseline and follow-up. Fasting insulin, 2-hour glucose, and triglycerides were logarithmically transformed owing to their skewed distributions (geometric mean and 95% confidence intervals are presented in the results). Associations between variables were examined using Pearson correlation coefficients and partial correlation coefficients.

To examine whether change in PAEE and change in FM (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 change in PAEE and change in FM 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 FM and the outcome variables were independent of baseline levels of PAEE and FM, 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 FM and baseline FM.

**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, FM, waist circumference, systolic and diastolic blood pressures, 2-hour glucose, fasting insulin, PAEE, and VO$_{2\text{max}}$ increased significantly, and FFM, decreased significantly in both genders 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. Prevalence of overweight and obesity were 43.1% and 14.5%, respectively in our cohort.

Change in PAEE was not significantly associated with change in FM ($r =0.02$, p=0.65) and 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 FM 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 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/kgFFM/min increase in PAEE from baseline to follow-up corresponded with a reduction in 2-h glucose by 3.2% (95% CI 0.33% to 5.3%) in men and of 3.1% (95% CI 0.33% to 5.2%) in women. For the same unit change in PAEE, fasting insulin was reduced by 5.3% (95% CI 1.0% to 7.5%) in both men and women, fasting triglycerides were reduced by 3.5% (95% CI 0.3% to 5.7%) in men and 3.2% (95% CI 0.2% to 5.4%) in women. There was also a 0.92 (95% CI 0.38 to 1.47) SD reduction in clustered metabolic risk. Change in FM was significantly and positively associated with diastolic BP, systolic BP, 2-h glucose, fasting insulin, triglycerides and clustered metabolic risk. For every 1 kg increase in FM from
baseline to follow-up, there was an associated 0.04 (95% CI 0.02 to 0.04) SD 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 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 FM with baseline FM (P = 0.43). No significant interaction (P = 0.2) was observed between change in PAEE and change in FM 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 aetiological 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 was included did not differ from those in which FM was included. Increase in waist circumference was significantly associated with the same individual risk factors as when FM was modelled as the exposure (data not shown).

The magnitude of the associations with change in PAEE and with change in FM for each of the risk factors were compared by including these variables as standardised z-scores from the baseline distribution. Similar to our original model, change in PAEE was significantly and inversely associated with fasting insulin, triglycerides and 2-hour glucose (P < 0.03) independent of change in FM and the same confounding factors as above. However, the magnitudes were generally 2 to 3 times greater for change in FM compared with change in PAEE (coefficients ranged from 0.12 to 0.19 for FM vs. -0.02 to -0.09 for PAEE).

We also attempted to account for residual confounding by obesity by reanalysing our data having normalised PAEE to body weight (instead of FFM) and by expressing PAEE in absolute values and additionally 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 FM.

We then excluded all individuals with diagnosed diabetes and IGT (n = 23) at baseline and reanalysed our data. The associations between change in PAEE and fasting insulin, and change in PAEE and triglycerides were unchanged, whereas a 1 kJ/kgFFM/min increase in PAEE during follow-up associated with a modest improvement in 2hr glucose (a reduction of 1.64 (95% CI 0.42; 2.84) SD; p=0.012). The associations between changes in FM were unchanged after exclusion of individuals with IGT and type 2 diabetes at baseline (data not shown).

**Figure 1** shows the association between change in PAEE and FM, 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 was associated with favourable metabolic risk scores across tertiles of FM.

**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 glycaemic 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 exercise intensity (13). Studies elsewhere have shown that moderate (14, 15) and vigorous exercise (16, 17) 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 et al (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 with the degree of measurement error for the physical activity variable; Hunter et al (22, 23), assessed physical activity by self-report and expressed it as an activity index on a scale from one to five. This method is less precise than objective measurements of PAEE and measurement error associated with subjective PA assessment increases with body weight (29). By contrast, a recent randomised control trial in overweight men and women with mild to moderate dyslipidaemia showed that the total volume, but not intensity, of exercise improved lipidaemia. 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 are 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 PAEE and aerobic fitness. Consistent with our observations, a recent cross-sectional study in healthy men concluded that higher fat mass associated with an adverse risk profile independently 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 minutes of brisk walking) was associated with a reduction of about 1 to 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 independently 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 when considering data from appropriately designed clinical trials. However, statistical models, such as those reported on here, where change in the independent variables is modelled 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 for confounding to persist in a change model requires that the confounder(s) change in a similar way as 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), which demonstrate that exercise training and lifestyle modification confers positive effects on a wide variety of metabolic traits.

An additional possible limitation of our study is that the individual calibration procedures for EE 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 characterised 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 sub maximal exercise test. Our sub-maximal measure of fitness is less precise than a true maximal test but was selected as it is feasible 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 importantly, it is unlikely that predicted fitness from our sub maximal 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-individual and intra-individual covariances in a repeated-measures sub-study, indicating that our sub maximal test is reliable.
over time (41). Similar to PAEE, it is unlikely 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 standardised z-scores from the baseline distribution and reanalysed 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, reduced body fat mass and irrespective of the initial levels of activity. However, body fatness was more strongly related to multiple metabolic risk factors and clustered metabolic risk than 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.

Acknowledgements
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References


Table 1. Descriptive characteristics (mean and SD, unless otherwise stated) of participants at baseline and follow-up (n = 393), The MRC Ely study, 1994 - 2003.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.7</td>
<td>8.0</td>
<td>55.3</td>
<td>8.2††</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.5</td>
<td>10.5</td>
<td>83.6</td>
<td>11.8††</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.7</td>
<td>6.2</td>
<td>175.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>18.9</td>
<td>5.4</td>
<td>21.3</td>
<td>6.3†††</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>63.6</td>
<td>6.7</td>
<td>62.4</td>
<td>7.3†††</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>94.1</td>
<td>8.6</td>
<td>97.9</td>
<td>9.0†††</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.0</td>
<td>10.6</td>
<td>82.0</td>
<td>10.9†††</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128.5</td>
<td>14.4</td>
<td>132.9</td>
<td>15.0†††</td>
</tr>
<tr>
<td>2-h glucose (mmol/l)</td>
<td>5.1 (4.9; 5.3)</td>
<td>6.0 (5.7; 6.3)</td>
<td>5.1 (4.9; 5.3)</td>
<td>5.7(5.5; 6.0)</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>41.1 (37.8; 44.7)</td>
<td>51.4 (46.7; 56.6)</td>
<td>35.7 (33.0; 38.5)</td>
<td>40.9 (37.7; 44.8)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.3 (1.2; 1.4)</td>
<td>1.3 (1.2; 1.4)</td>
<td>1.0 (1.0; 1.1)</td>
<td>1.1 (1.0; 1.2)</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.33</td>
<td>0.35</td>
<td>1.31</td>
<td>0.33</td>
</tr>
<tr>
<td>VO2max (ml kgFFM⁻¹ min⁻¹)</td>
<td>46.8</td>
<td>10.8</td>
<td>57.9</td>
<td>14.1†††</td>
</tr>
<tr>
<td>PAEE (kJ kgFFM⁻¹ min⁻¹)</td>
<td>0.12</td>
<td>0.05</td>
<td>0.16</td>
<td>0.07†††</td>
</tr>
</tbody>
</table>

†geometric means and 95% CI, HDL, High density lipoprotein, ANOVA for between sex differences: ***P < 0.001
ANOVA for between time differences: ††P < 0.01; †††P < 0.001
No significant time by sex interactions were observed
Table 2. Independent associations between change in PAEE and individual metabolic risk factors and clustered metabolic risk 5.6 years later, and between change in FM and individual metabolic risk factors and clustered metabolic risk 5.6 years later. Data are regression coefficients (95% CI), which represent the expected change in the outcome (expressed as a standardised z score) for a 1 unit increase in either change in PAEE or change in FM. (n=393)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change in PAEE</th>
<th>P</th>
<th>Change in FM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>-0.88 (-1.79;0.04)</td>
<td>0.06</td>
<td>0.04 (0.03;0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-0.68 (-1.62;0.27)</td>
<td>0.16</td>
<td>0.04 (0.02;0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-h glucose (mmol l⁻¹)</td>
<td>-1.40 (-2.70;-0.10)</td>
<td>0.035</td>
<td>0.03 (0.008;0.05)</td>
<td>0.008</td>
</tr>
<tr>
<td>Insulin (mU l⁻¹)</td>
<td>-1.32 (-2.46;-0.18)</td>
<td>0.023</td>
<td>0.06 (0.04:0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol l⁻¹)</td>
<td>-0.88 (-1.76;-0.003)</td>
<td>0.049</td>
<td>0.03 (0.02;0.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL (mmol l⁻¹)</td>
<td>0.21 (-0.56;0.98)</td>
<td>0.60</td>
<td>-0.01 (-0.02;0.003)</td>
<td>0.14</td>
</tr>
<tr>
<td>Clustered metabolic risk</td>
<td>-0.92 (-1.47;-0.38)</td>
<td>0.001</td>
<td>0.04 (0.03;0.04)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HDL, High density lipoprotein, BP, Blood Pressure
Fasting insulin, triglycerides and 2-hour 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 FM are included in the same model
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 and physical activity (squares = top tertile of PAEE; circles = mid tertile of PAEE; triangles = 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).