Physical Activity and Metabolic Risk in Individuals With a Family History of Type 2 Diabetes

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OBJECTIVE — We sought to examine the independent associations between different dimensions of physical activity with intermediary and clustered metabolic risk factors in overweight individuals with an increased risk of type 2 diabetes to inform future preventive action.

RESEARCH DESIGN AND METHODS — We measured total body movement and five other subcomponents of physical activity by accelerometry in 258 adults (aged 30–50 years) with a family history of type 2 diabetes. We estimated aerobic fitness from an incremental treadmill exercise test. We measured body composition by bioimpedance and waist circumference, blood pressure, fasting triglycerides, HDL cholesterol, glucose, and insulin with standard methods. We constructed a standardized continuously distributed variable for clustered risk.

RESULTS — Total body movement (counts · day^{-1}) was significantly and independently associated with three of six risk factors (fasting triglycerides, insulin, and HDL) and with clustered metabolic risk ($P = 0.004$) after adjustment for age, sex, and obesity. Time spent at moderate- and vigorous-intensity physical activity (MPVA) was independently associated with clustered metabolic risk ($P = 0.03$). Five- and 10-min bouts of MVPA, time spent sedentary, time spent at light-intensity activity, and aerobic fitness were not significantly related with clustered risk after adjustment for confounding factors.

CONCLUSIONS — Total body movement is associated with intermediary phenotypic risk factors for cardiovascular disease and metabolic disease and with clustered metabolic risk independent of aerobic fitness and obesity. Increasing the total amount of physical activity in sedentary and overweight individuals may have beneficial effects on metabolic risk factors.

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The metabolic syndrome is loosely defined as a cluster of cardiovascular disease (CVD) risk factors, including disturbed insulin and glucose metabolism, hypertension, abdominal obesity, and dyslipidemia. This syndrome predicts the development of type 2 diabetes, CVD, and all-cause mortality (1,2). Low levels of physical activity are believed to be an important determinant of this cluster of metabolic risk factors. Given the global increase in the prevalence of obesity, type 2 diabetes, and the metabolic syndrome (3–6), there is a need to further understand how intermediary phenotypic metabolic risk factors are influenced by potentially modifiable lifestyle behaviors, such as physical activity.

Total body movement (i.e., the total amount of physical activity) and patterns of activity (i.e., time spent sedentary and at various intensity levels and bouts of sustained activity) are separate dimensions of activity, which may be associated with intermediary phenotypes of metabolic risk in different ways. However, these subdimensions of activity are inherently difficult to measure precisely in epidemiological studies because of their complex and latent nature (7). Previous researchers have primarily relied on self-reported physical activity when examining associations between physical activity and clustered metabolic risk and its subcomponents (8–14). We have recently suggested that objectively measured physical activity energy expenditure (PAEE) is independently associated with clustered metabolic risk in a healthy population (15) and that PAEE predicts progression to the metabolic syndrome independent of aerobic fitness and body fatness (16). However, it was unclear from these studies which, if any, of the subdimensions of physical activity exert a greater influence on individual and clustered metabolic risk factors. Given that strategies to promote distinct types of physical activity will differ, it is important to understand the dimensions of activity most strongly associated with a particular outcome when one is designing preventive interventions for high-risk groups. Targeting the wrong dimensions of physical activity may limit the potential benefits predicted by observational studies.

The purpose of the present study was to examine the magnitude and directions of associations between total body movement; accumulated time spent sedentary, at light-intensity activity, and at moderate- and vigorous-intensity physical activity (MVPA); and bouts of MVPA with established metabolic risk factors to inform future preventive action. This cross-sectional study was conducted in healthy men and women at high risk of developing type 2 diabetes because of a family history of the disease.

RESEARCH DESIGN AND METHODS

Individuals in the study population were all participants in the ProActive Study, a randomized, controlled trial examining the efficacy of a family-based intervention to increase physical activity among individuals defined as high-risk through having a parental history of type 2 diabetes. The selection procedures, screening, recruitment, inclusion criteria, randomization, design, and methods have been described

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Abbreviations: CVD, cardiovascular disease; FFM, fat-free mass; MVPA, moderate- and vigorous-intensity physical activity; PAEE, physical activity energy expenditure.
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previously (17). Briefly, potential participants were identified via diabetes registers and medical records of family history in 20 general practices in East Anglia. To exclude very active individuals, participants completed a screening activity questionnaire describing occupational and leisure activity, based on published questionnaires (18,19).

Of the 465 eligible individuals, 399 were recruited for baseline measurements. Complete data on aerobic fitness, anthropometrics, and biochemistry at baseline were available for 365 individuals. In a subsample ($n = 258$), patterns of physical activity were also measured objectively by means of accelerometry. This constitutes the sample for the present analyses. All data presented in this report are cross-sectional data from the baseline data collection conducted before randomization. All participants provided written informed consent, and ethical permission for the study was granted by the Eastern England Multicenter Research Ethics Committee.

Anthropometric and metabolic tests

Height and weight were measured using a rigid stadiometer and calibrated scales with the subjects wearing light clothing. Waist circumference was measured in duplicate using a metal tape. Resistance (ohms) was assessed using a standard bioimpedance technique (Bodystat, Isle of Man, U.K.). This method has previously been shown to be valid (20) and reliable (21). Total body water and fat-free mass (FFM) were calculated using the impedance index (square of height divided by resistance), and body weight and resistance were calculated according to published equations (22). Fat mass was calculated as body weight minus FFM. Percent body fat was calculated as fat mass/body weight × 100.

Blood pressure was measured with subjects 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.

Fasting blood samples were taken, centrifuged and aliquoted on site, and immediately placed on 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 a 1235 AutoDELFIA automatic immunoassay system using a two-step time-resolved fluorometric assay (DAKO, Ely, Cambridgeshire, U.K.). Cross-reactivity with intact proinsulin is <0.5% at 2,736 pmol/l, with 32–33 split proinsulin is 1% at 2,800 pmol/l, and with C-peptide is <0.1% at 5,280 pmol/l. Typical interassay coefficients of variance are 3.1% at 29.0 pmol/l, 2.1% at 79.4 pmol/l, 1.9% at 277 pmol/l, and 2.0% at 705 pmol/l, respectively ($n = 174$ in each case).

Clustered metabolic risk

We constructed a standardized continuously distributed variable (*zMS*) for clustered metabolic risk, which we have described in detail previously (15,16). This variable was derived by standardizing and then summing the following continuously distributed indexes of obesity (waist circumference), hypertension ([systolic blood pressure + diastolic blood pressure]/2), hyperglycemia (fasting plasma glucose), insulin resistance (fasting insulin), inverted fasting HDL cholesterol, and hypertriglyceridemia to create a *Z* score. The purpose of using a continuously distributed variable was to maximize statistical power (23).

Assessment of aerobic fitness and physical activity

Aerobic fitness ($V\text{O}_{2\text{max}}$) was predicted as oxygen uptake at maximal heart rate (220 minus age) by extrapolation of the regression line established during the individual calibration for the relationship between oxygen consumption and heart rate during a submaximal graded treadmill exercise test. Oxygen uptake and CO_2 production were continuously measured by indirect calorimetry throughout the test (Vista XT metabolic system; Vacumed, Ventura, CA). Participants breathed through a face mask (Hans Rudolph, Kansas City, MO), and expired air was measured with a turbine flowmeter, carbon dioxide concentration with an infrared sensor, and oxygen concentration with a fast differential paramagnetic sensor. Gas analyzers were calibrated with gases of known composition, and the turbine flow meter was calibrated with a 3-l syringe before each measurement.

Data on free-living physical activity was assessed with an MTI ActiGraph (formerly known as the CSA activity monitor) model WAM 7164 (Manufacturing Technology, Fort Walton Beach, FL) accelerometer over 4 consecutive days. The participants wore the accelerometer in an elastic waistband at the lower back during daytime, except while bathing and during other aquatic activities. Participants who did not manage to record at least 500 min/day of activity for at least 3 days were excluded from further analyses ($n = 7$). The outcome variables were total body movement (counts · day^{-1}), which is an indicator of the total volume of physical activity, and time (minutes · day^{-1}) spent at different activity intensity categories averaged per day over the measurement period. These were calculated to determine which subcomponents of activity, if any, are associated with individual and clustered metabolic risk and to establish whether these associations were related in a dose-response manner. Intensity thresholds for moderate (1,952–5,724 counts · min^{-1}) and vigorous intensity activity (>5,725 counts · min^{-1}) were defined according to Freedson et al. (24). Because >60% of participants did not accumulate any time in vigorous intensity physical activity, we constructed a single variable by combining accumulated time in MVPA. Sedentary behavior was defined as <100 counts · min^{-1} and light intensity activity as 101–1,951 counts · min^{-1}. The cutoff for sedentary behavior is an arbitrary threshold, which we have used previously (25). We also calculated the average number of 5- and 10-min bouts of sustained physical activity at the MVPA level. In these analyses we allowed 1 min to drop below the threshold for MVPA in each 5-min bout. We calculated the percentage of participants accumulating 30 min or more per day at MVPA according to the recommendations from the Centers for Disease Control and Prevention and the American College of Sports Medicine (26). Data reduction, cleaning, and analyses of accelerometer data were performed using a specially written program (MAHUffe; see www.mrc-epid.cam.ac.uk).

Statistics

Descriptive summary statistics were calculated using means ± SD. Fasting insulin and triglycerides were logarithmically transformed owing to their skewed distribution. Geometric mean and reference intervals (1.96 × SD) are presented in the RESULTS.

We modeled the associations be-

Table 1—*Descriptive characteristics of participants*

	Men	Women	*P* value by ANOVA
n	103	155	
Age (years)	40.9 ± 6.4	40.7 ± 6.4	NS
Weight (kg)	90.4 ± 16.4	73.7 ± 14.4	<0.0001
Height (m)	1.78 ± 0.07	1.64 ± 0.06	<0.0001
BMI (kg/m^2)	28.4 ± 4.6	27.4 ± 5.1	NS
Fat mass (kg)	22.5 ± 9.4	26.6 ± 10.0	0.01
FFM (kg)	67.9 ± 8.7	47.1 ± 6.2	<0.0001
Waist (cm)	101.4 ± 12.0	88.1 ± 11.8	<0.0001
Systolic blood pressure (mmHg)	127.3 ± 11.2	120.8 ± 13.6	<0.0001
Diastolic blood pressure (mmHg)	81.9 ± 8.8	76.2 ± 9.3	<0.0001
Fasting insulin (mmol · l^{-1})	55.7 (50.2–61.8)	46.5 (43.4–49.8)	0.02
Fasting glucose (mmol · l^{-1})	5.10 ± 0.86	4.78 ± 0.52	<0.0001
Triglycerides (mmol · l^{-1})	1.45 (1.31–1.61)	1.05 (0.98–1.11)	<0.0001
HDL (mmol · l^{-1})	1.22 ± 0.32	1.57 ± 0.38	<0.0001
$V\text{O}_{2\text{MAX}}$ (ml·FFM · min^{-1})	59.6 ± 11.1	57.8 ± 10.4	NS
Time sedentary (min · day^{-1})	442 ± 97	419 ± 77	0.03
Time light (min · day^{-1})	309 ± 80	320 ± 68	NS
Time moderate and vigorous (min · day^{-1})	30 ± 18	24 ± 16	0.003
No. of 5-min bouts of MVPA	0.9 ± 0.9	0.8 ± 0.9	NS
No. of 10-min bouts of MVPA	0.3 ± 0.5	0.2 ± 0.4	NS
Total counts (× 1,000 · day^{-1})	283 ± 104	264 ± 98	NS

Data are means ± SD or geometric mean (95% CI). *n* = 258.

tween all physical activity subcomponents (total counts, time spent sedentary, at light intensity activity, and at MVPA, and bouts of MVPA) and the phenotypes of the metabolic syndrome and clustered metabolic risk in separate models. These analyses were adjusted for age and sex. When obesity was not the outcome of interest, we assessed whether the subcomponents of physical activity were associated with each intermediary phenotype per se after adjustment for waist circumference, age, and sex. We then examined whether the different physical activity subcomponents were associated with clustered metabolic risk (*zMS*) in separate models. Finally, stepwise multiple linear regression analysis was used to examine which of the accelerometry-derived time estimates of physical activity variables contributed to the explained variation in clustered metabolic risk after adjustment for sex, age, and measurement time. We controlled for multicollinearity by calculating the correlation coefficients between the different time-derived variables and by calculating the tolerance and variance inflation factors. All data were analyzed in their continuous form although data are stratified by quartiles of total body movement (counts · day^{-1}) 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 descriptive characteristics of study participants. Thirty-two percent of participants were classified as normal weight, 40% were overweight, and an additional 27% were obese. Age, weight, height, BMI, waist circumference, fat mass, FFM, $V\text{O}_{2\text{max}}$, fasting HDL cholesterol, triglycerides, glucose, and the summary score of clustered metabolic risk did not differ significantly (all $P > 0.15$) between those included in this report ($n = 258$) and the rest of the study participants ($n = 105$). However, fasting insulin (log transformed) was slightly higher in those included in the present report ($P = 0.041$).

Sex differences were observed for most of the body composition and metabolic variables. Aerobic fitness and total body movement (total counts per day) were similar for men and women. However, they allocated their physical activity differently between the different time estimates of activity. Men spent significantly more time sedentary ($P = 0.03$) and at MVPA ($P = 0.002$) than women. Two-thirds (66.2%) of participants accumulated <30 min of MPVA per day according to the accelerometry measurements. Of participants, 61 and 25% did not record any single 10- or 5-min bouts, respectively, of MVPA during the measurement period.

Table 2 shows the separate associations (standardized β-coefficients) between accumulated time spent sedentary, at light intensity activity, and at MVPA and total body movement (counts · day^{-1}), with the intermediary phenotypic metabolic risk factors and clustered metabolic risk. Because all outcomes are expressed in the same unit (SD), it is possible to directly compare the magnitude of associations between the different components of activity to each of the outcomes, assuming they are measured with the same degree of measurement error. Total body movement (counts · day^{-1}) was significantly and independently associated with three (fasting insulin, triglycerides, and HDL cholesterol) of the six individual risk factors and with clustered metabolic risk. Time spent sedentary was marginally significantly associated with fasting insulin ($P = 0.05$). Time spent at light-intensity activity was inversely associated with fasting triglycerides ($P = 0.03$). Time spent at MVPA was significantly associated with fasting insulin ($P = 0.02$) and clustered metabolic risk ($P = 0.03$). As indicated by the β-coefficients, the magnitude of association between total body movement (counts · day^{-1}) with clustered metabolic risk was about 25% stronger than that between MVPA and clustered risk. Bouts of PA were not significantly associated with any of the intermediary risk factors or with clustered metabolic risk (data not shown). Furthermore, substituting waist circumference

Table 2—*Independent associations of patterns of physical activity from accelerometry and intermediary phenotypic risk factors and clustered metabolic risk in middle-aged adults with a family history of type 2 diabetes*

Outcome	Sedentary	*P* value	Light	*P* value	MVPA	*P* value	Total counts	*P* value	Fitness	*P* value
Waist (cm)	0.04 (−0.07 to 0.14)	0.51	0.03 (−0.08 to 0.13)	0.63	−0.10 (−0.21 to 0.01)	0.07	−0.09 (−0.20 to 0.01)	0.09	0.005 (−0.003 to 0.013)	0.21
Blood pressure	0.02 (−0.09 to 0.12)	0.77	−0.02 (−0.12 to 0.09)	0.75	−0.03 (−0.14 to 0.07)	0.53	−0.03 (−0.14 to 0.08)	0.59	−0.005 (−0.1 to 0.002)	0.17
Insulin (mol $\cdot$ l^{-1})	0.10 (0.001–0.19)	0.049	−0.06 (−0.18 to 0.07)	0.40	−0.12 (−0.21 to −0.02)	0.02	−0.14 (−0.23 to −0.04)	0.005	−0.01 (−0.02 to −0.004)	0.003
Glucose (mmol $\cdot$ l^{-1})	−0.02 (−0.13 to 0.09)	0.73	0.03 (−0.08 to 0.14)	0.60	0.05 (−0.06 to 0.16)	0.37	0.002 (−0.11 to 0.11)	0.97	−0.003 (−0.01 to 0.005)	0.50
Triglycerides (mmol $\cdot$ l^{-1})	0.08 (−0.04 to 0.20)	0.20	−0.12 (−0.23 to −0.001)	0.03	−0.06 (−0.18 to 0.05)	0.27	−0.12 (−0.23 to −0.003)	0.04	−0.004 (−0.01 to 0.004)	0.30
Inverted HDL (mmol $\cdot$ l^{-1})	0.10 (−0.01 to 0.21)	0.08	−0.06 (−0.17 to 0.05)	0.28	−0.07 (−0.17 to 0.03)	0.17	−0.11 (−0.20 to −0.001)	0.03	0.002 (−0.005 to 0.009)	0.56
Sum Z scores	0.07 (−0.01 to 0.14)	0.10	−0.03 (−0.12 to 0.05)	0.40	−0.09 (−0.17 to −0.008)	0.03	−0.12 (−0.20 to −0.04)	0.004	−0.003 (−0.007 to 0.001)	0.09

Data are standardized β-coefficients (95% CI). $n = 258$. Data on insulin and triglycerides are log transformed. Data are adjusted for sex and age. Data on total counts from accelerometry are additionally adjusted for monitoring time. All subcomponents except waist circumference are additionally adjusted for waist circumference.

with fat mass or BMI as a confounding variable did not change the results (data not shown). Similarly, when we excluded waist circumference for the clustered risk score and adjusted for waist circumference as a confounder, the results were unchanged (data not shown).We reexamined our data for the associations between total body movement with individual and clustered metabolic risk by further adjustment for aerobic fitness, and the results were unchanged (data not shown).

Finally, we examined which of the time estimates (i.e., time spent sedentary, at light-intensity activity, and at MVPA) contributed to the explained variance in clustered metabolic risk after adjusting for age, sex, and aerobic fitness. Time spent at MVPA (standardized $\beta = -0.13$ [95% CI -0.17 to -0.01], $P = 0.03$) and sex remained as significant explanatory variables in the final model (adjusted $R^2 = 19.1\%$). Aerobic fitness was significantly and inversely associated with fasting insulin ($P = 0.003$) but not with any of the other individual risk factors or with clustered metabolic risk (Table 2).

Figure 1 shows the associations between total body movement (counts $\cdot$ day^{-1}) and clustered metabolic risk. A significant inverse dose-response association was observed between quartiles of total activity with clustered metabolic risk (P for trend $= 0.02$).

CONCLUSIONS — We show here the cross-sectional associations between different subcomponents of objectively measured physical activity with intermediary phenotypic risk factors and clustered metabolic risk in a group of sedentary, middle-aged individuals with a family history of type 2 diabetes. Our results suggest that total body movement was significantly associated with insulin resistance, dyslipidemia, and clustered metabolic risk independent of sex, age, obesity, and aerobic fitness. Time spent at MVPA was weakly associated with clustered risk, whereas bouts of MVPA and accumulated time spent sedentary and at light-intensity activity were unrelated to clustered risk. Promoting overall body movement and an increase in everyday total physical activity may therefore have beneficial effects on metabolic risk factors in overweight, sedentary adults.

There are several limitations that need to be considered when interpreting the findings from this study. First, this is a cross-sectional study, limiting inferences of causality and its direction. Although we controlled for several potential confounding factors (sex, age, aerobic fitness, and obesity), it is possible that other unmeasured confounders, such as genetic variation, socioeconomic variables, and early life programming, could explain our findings. Second, our results may be restricted to sedentary, overweight, middle-aged, Caucasian individuals with a family history of type 2 diabetes. However, given the epidemic increase in overweight and obesity (3) and the large proportion of adults who are not sufficiently active (27), it is likely that our results are generalizable to a large part of the general population. Third, the low frequency of individuals participating in vigorous-intensity physical activity may reduce the power to observe associations between time spent at this intensity level and metabolic risk.

This study also has unique strengths. We reduced the potential for recall bias and differential measurement error, which is an unavoidable component of self-reported physical activity, by measuring the total volume and other subcomponents of activity with accelerometry. These methods have been extensively validated in the laboratory and during free-living conditions (24,28–30). Aerobic fitness was derived from a submaximal exercise test. This measure is less precise than a true maximal exercise test. However, it is unlikely that this fact will bias the results of the present study, as the error in predicted maximal heat rate is likely to be random across the cohort. It is therefore also unlikely that the observed associations between activity variables, aerobic fitness, and metabolic outcomes are due to chance, bias, or measurement error.

The association between total body movement and clustered metabolic risk was ~25% stronger than the association between time spent at MVPA and clustered risk. This result supports the argument that all body movements that contribute to elevated energy expenditure contribute to a favorable metabolic risk profile. This observation is important when one is translating epidemiological findings into preventive action. Thus, although structured exercise and moderate to vigorous activity contribute to the prevention of cardiovascular and metabolic disease risk, particularly among those at high risk (31), an exclusive focus on increasing vigorous activity and structured exercise could have counterintuitive consequences, especially in populations who

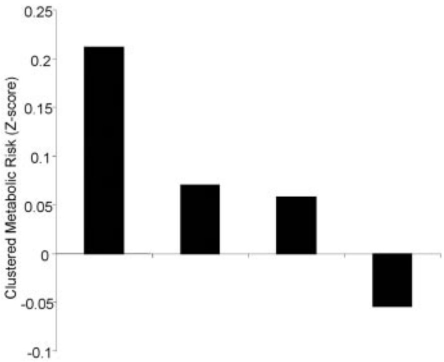

Figure 1—*Clustered metabolic risk score stratified by quartiles of the total amount of activity (counts · day^{-1} × 1,000) by accelerometry in sedentary, overweight, middle-aged men and women at high risk of developing diabetes* (n = 258)*. Data are adjusted for sex, age, and monitoring time (*P *for trend = 0.02).*

find these activities unattractive and these targets hard to reach. Our results corroborate our previous findings suggesting that higher levels of PAEE measured by individual calibrated heart rate monitoring are favorably associated with features of the metabolic syndrome (15,16).

Study participants recorded, on average, fewer than one 5-min bout of MVPA per day, and bouts of MVPA were not associated with any of the intermediary phenotypic risk factors. It may be that the accumulated time at MVPA and particularly total body movement is more important in relation to these risk factors in sedentary individuals. However, we cannot exclude the possibility that bouts of activity are more strongly associated with intermediary phenotypic risk factors in a more heterogeneous population. Our data also suggest a linear dose-response association between the total amount of activity with clustered metabolic risk. Thus, sedentary individuals may benefit from accumulating physical activity throughout the day or in shorter bouts (i.e., <5 min), and more activity accumulated leads to greater metabolic health benefits.

Previous epidemiological studies have clearly demonstrated that self-reported physical activity predicts cardiovascular morbidity and mortality end points (32–34) and that both walking and vigorous exercise are associated with risk reduction in the incidence of cardiovascular events (35–37). Further, both physical activity and obesity are independent predictors of all-cause mortality (38). However, these studies have not been able to characterize minute-by-minute patterns of physical activity because of reliance on self-reported measures of activity and lack of controls for aerobic fitness. From a public health perspective, this fact is important because if the association between physical activity and CVD and metabolic risk factors is mediated through aerobic fitness, it is likely that more vigorous exercise is needed to prevent CVD morbidity and mortality. Individual and population-based interventions would need to reflect this possibility.

In summary, total body movement is associated with intermediary phenotypic risk factors for CVD and metabolic disease and with clustered metabolic risk independent of aerobic fitness and obesity. Increasing the total amount of physical activity in sedentary and overweight individuals may have beneficial effects on these metabolic risk factors.

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