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A quantitative analysis of the relationship between habitual energy expenditure, fitness and the metabolic cardiovascular syndrome

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Previous epidemiological studies have suggested an association between low levels of physical activity, fitness and the metabolic cardiovascular syndrome. However, many studies have used subjective non-quantitative questionnaire-based methods for assessing physical activity which do not distinguish between the different dimensions of this complex exposure, and in which measurement error in the exposure has not been estimated. These deficiencies in the measurement of this exposure complicate the interpretation of the results of epidemiological studies, and consequently make it difficult to design appropriate interventions and to estimate the expected benefit which would result from intervention. In particular, it is unclear whether public health advice should be to increase total energy expenditure, or to attempt to raise fitness by recommending periods of vigorous activity. To separate the effects of fitness and total energy expenditure in the aetiology of the metabolic cardiovascular syndrome, we measured the physical activity level (PAL), defined as total energy expenditure : BMR, and fitness (maximum O_2 consumption (V_{O_2max} per kg), measured in a sub-maximal test) in a cross-sectional population-based study of 162 adults aged 30–40 years. Heart-rate monitoring with individual calibration was used to measure total energy expenditure using the HRFlex method (Ceesay *et al*. 1989) which has been validated previously against doubly-labelled water and whole-body calorimetry. The relationship between a single measure of PAL, V_{O_2max} per kg and the usual or habitual level for each exposure was measured in a sub-study of twenty-two subjects who undertook four repeated measures over the course of 1 year. This study design allows the reliability coefficient to be computed, which is used to adjust the observed associations for measurement error in the exposure. Twelve men (16·4 %) and sixteen women (18·0 %) were defined as having one or more features of the metabolic cardiovascular syndrome. The univariate odds ratio for each increasing quartile for PAL was 0·64 (95 % CI 0·43–0·94) and was 0·49 (95 % CI 0·32–0·74) for V_{O_2max} per kg, suggesting that the association with the metabolic cardiovascular syndrome was stronger for fitness than for PAL. However, after adjustment for obesity and sex, and correction for exposure measurement error, the odds ratio per quartile for PAL was 0·32 (95 % CI 0·13–0·83) and 0·44 (95 % CI 0·24–0·78) for V_{O_2max} per kg. Thus, although univariate analysis would suggest that fitness has a stronger association with the metabolic cardiovascular syndrome than PAL, this conclusion is reversed once confounding and the differences in measurement error are considered. We conclude from the present study that the metabolic cardiovascular syndrome is strongly associated with reduced habitual energy expenditure. The method employed to assess the exposure in the present study demonstrates the utility of assessing a known dimension of physical activity using a physiologically-based and objective measure with repeated estimation to adjust for measurement error. Such quantitative epidemiological data provide the basis for planning and evaluating the expected benefit of population-level interventions.

Physical activity: Fitness: Energy expenditure: Metabolic cardiovascular syndrome

Abbreviations: PAL, physical activity level; V_{O_2max}, maximum oxygen consumption; $\hat{\rho}$, reliability coefficient.

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Physical activity is a complex and difficult exposure to measure in epidemiological studies. Most studies have relied on measures derived from self-reported behaviour, and have concentrated on participation in sports and recreations as these are discrete, and therefore easily recalled, activities (Paffenbarger *et al*. 1993). Although such simple measures have been useful in demonstrating associations with many chronic disease end points, this simplicity has complicated the transfer of epidemiological information into public health recommendations. As the methods are non-quantitative, it is difficult to extrapolate from these observations to answer questions about how much activity is of benefit. Furthermore, it is not clear which dimension of physical activity these measures are assessing. Thus, for example, it would be impossible to conclude from current evidence whether improved fitness or increased total energy expenditure was more closely associated with a given health outcome. This uncertainty makes it important to continue the search for objective and well-validated quantitative methods which assess a known dimension of physical activity, and which are applicable to epidemiological studies.

We have recently demonstrated that heart-rate monitoring with individual calibration (the HRFlex technique) is a feasible technique for assessing total energy expenditure in field studies (Wareham *et al*. 1997). The HRFlex method uses an individual calibration of the linear relationship between energy expenditure and heart rate on exertion, together with measurement of resting energy expenditure, and an assessment of the heart rate at which the linear assumption does not hold (the FLEX point). This FLEX heart rate is empirically defined as the mean of the highest heart rate at rest and the lowest on exercise (Ceesay *et al*. 1989). The method has been validated previously by comparison with the doubly-labelled-water method and whole-body calorimetry (Spurr *et al*. 1988; Ceesay *et al*. 1989; Livingstone *et al*. 1990, 1992). In the present paper we report the use of that technique to estimate the relationship between habitual or usual energy expenditure and the metabolic cardiovascular syndrome. This syndrome is a loosely-defined cluster of metabolic abnormalities, including hypertriacylglycerolaemia, lowered HDL-cholesterol, glucose intolerance and hypertension (Haffner *et al*. 1992*b*). As these abnormalities are often correlated with insulin resistance, it has been suggested that the latter may be the underlying cause for this clustering (Reaven, 1988). We have elected to use the descriptive term the metabolic cardiovascular syndrome for this cluster, although other researchers use other terms, e.g. syndrome X or insulin-resistance syndrome. Individuals with metabolic cardiovascular syndrome are at risk of developing type II diabetes and cardiovascular disease (Haffner *et al*. 1992*a*). The aetiology of this syndrome remains uncertain, partly because of difficulties in disease definition. It has been suggested that low physical activity may be an important aetiological factor (Eriksson *et al*. 1997), but previous studies have used non-quantitative methods for assessing the exposure.

The true exposure of interest in the present study is the usual level of energy expenditure, which is an unmeasurable or latent variable. It is common in epidemiology to take a single measure of a given exposure and then to assume that this reflects the usual or habitual level. For variables which are measured precisely and which do not have a high degree of inherent variability, this assumption is valid. However, if an exposure is both difficult to measure and also inherently variable, then a single measure will estimate the usual level with considerable imprecision. This imprecision has an effect on the observed association between this exposure and any given outcome. If the imprecision is random, the effect is to diminish the observed association. If the error is non-random, the effect can be more unpredictable (Armstrong *et al*. 1994). This problem is highly relevant to the situation of estimating the true association between energy expenditure and a disease state. If one takes a single estimate of energy expenditure, then, assuming that the error is non-differential, the observed association that is seen will be smaller than the truth. This effect is known as the regression-dilution bias, and it leads to the underestimation of the association between a disease outcome and exposures which are variable and difficult to measure.

It is possible to adjust an association between energy expenditure and a given outcome for the regression-dilution bias, provided one knows the degree of imprecision in the measurement of exposure (MacMahon *et al*. 1990; Armstrong *et al*. 1994). If the true exposure is denoted as T, then it is estimated in an epidemiological study by an imperfect measurement X. By conventional measurement theory (Armstrong *et al*. 1994), the validity coefficient is the correlation between this imperfect measure and the true exposure denoted as ρ_{TX}. It is not usually possible to directly measure the true exposure of interest, but the parameter $\hat{\rho}_{TX}$ can be estimated indirectly. The correlation between independent repeated measurements of X, X_1 and X_2, is known as the reliability coefficient, ρ_{x1x2}, and the validity coefficient is given by the square root of the reliability coefficient, i.e. $\rho^2_{TX} = \rho_{x1x2}$. It can be shown that the relationship between the observed odds ratio (OR_O) in a case–control study is equal to the true odds ratio (OR_T) raised to the power of the square of the validity coefficient ($OR_O = OR_T^{\rho^2_{TX}}$). In the case of continuous data, the observed regression coefficient (β_O) is the product of the true regression coefficient (β_T) and the validity coefficient ($\beta_O = \rho^2_{TX}\beta_T$). Thus, provided the validity coefficient can be estimated from a reliability study, the true measure of effect can be computed from an observed association in an epidemiological study.

The present paper describes the findings of a study established to estimate the association between habitual energy expenditure, fitness and the metabolic cardiovascular syndrome, in which the observed association with a single measure of both fitness and energy expenditure has been adjusted for the regression-dilution bias using data from a repeated-measures sub-study.

Subjects and methods

Selection of the subjects

The overall study design has been described previously (Wareham *et al*. 1997). However, in brief, the cohort of 164 volunteers were recruited from a randomly selected

population-based sampling frame (response rate 50·8 %). Volunteers were invited to attend the clinic at 08.30 hours, having fasted since 22.00 hours the previous evening, and underwent a standard 75 g oral glucose tolerance test (World Health Organization Study Group, 1985). Ethical permission for the study was granted by the Cambridge District Ethics Committee.

Biochemical methods

Blood samples were taken at fasting, and 30 and 120 min following oral glucose. Plasma glucose was measured in the routine NHS laboratory at Addenbrooke's Hospital using the hexokinase (*EC* 2.7.1.1) method (Kunst *et al*. 1983), and total serum cholesterol, HDL and triacylglycerol using the RA 1000 (Bayer Diagnostics, Basingstoke, Hants., UK). Values for LDL-cholesterol concentrations were calculated using the Friedewald formula (Friedewald *et al*. 1972). Estimations were not made if plasma triacylglycerol was > 4 mmol/l. Blood samples were immediately placed in ice and centrifuged on site in a cooled centrifuge at 2500 rev./min. Serum samples were left for at least 30 min out of ice before being centrifuged. Aliquot samples were then transferred on ice to the Department of Clinical Biochemistry, Addenbrooke's Hospital, where they were stored at −70° until analysis was undertaken. Plasma insulin was measured using an immunoenzymetric assay (Medgenix Diagnostics SA, Fleurus, Belgium). Plasma intact and 32, 33 split proinsulin concentrations were measured using immunoradiometric assays (Sobey *et al*. 1989). These specific insulin precursor molecules have been shown previously to be elevated in subjects with glucose intolerance (Hales *et al*. 1996). Each of the four cardinal features of the metabolic cardiovascular syndrome were dichotomized according to the classification suggested by Haffner *et al*. (1992*b*). Hypertension was defined as diastolic blood pressure ≥95 mm Hg and/or currently on treatment for hypertension. Hypertriacylglycerolaemia was defined as a fasting serum triacylglycerol of > 2·82 mmol/l. Low-HDL cholesterol was defined as being < 0·91 mmol/l in men and < 1·17 mmol/l in women. The cut-off for glucose intolerance was a 2 h plasma glucose concentration of ≥7·8 mmol/l. For the purposes of this analysis, individuals were classified as having the metabolic cardiovascular syndrome if they had one or more of these metabolic features.

Anthropometric measurements

Height and weight were measured in light clothing. Body circumferences were measured in duplicate using a metal tape (CMS Weighing, London, UK). The waist circumference was measured at the mid-point between the lower costal margin and the level of the anterior superior iliac crest. Hip circumference was measured at the level of the greater trochanter. Body fat percentage was obtained using a standard impedance technique (Bodystat, Douglas, Isle of Man, UK).

Assessment of resting and exercise oxygen consumption–heart rate relationship

This part of the study protocol has been described previously in detail (Wareham *et al*. 1997). The O_2 consumption–heart rate relationship was assessed at rest with the subject lying prone and then seated, using an O_2 analyser (PK Morgan Ltd., Gillingham, Kent, UK) calibrated daily using 100 % N_2 and fresh air as standard gases. Subjects bicycled on a cycle ergometer at several different workloads to provide the slope and the intercept of the line relating energy expenditure to heart rate. Each subject cycled at 50 rev./min and the workload was progressively increased from 0 W, through 37·5 W, 75 W and 125 W in stages each lasting 5 min. At each workload three separate readings were made of heart rate, minute volume and expired-air O_2 concentration. The 125 W level was only undertaken if the heart rate had not reached 120 beats/min by the end of the 3 min at 75 W.

The O_2 concentration in the expired air and minute volume data were used to calculate O_2 consumption after correction for standard temperature and pressure. Energy expenditure (kJ/min) was calculated at each time point as O_2 consumption (ml/min) × 20·35 (Consolazio *et al*. 1963). Mean resting energy expenditure was taken as the average of the lying and sitting values. FLEX heart rate was calculated as the mean of the highest resting pulse rate and the lowest on exercise. Finally, the slope and intercept of the least squares regression line of the exercise points were calculated. These calculations were computed using an SPSS syntax file (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA). Maximum O_2 consumption (V_{O_2max}) was measured from the linear regression as predicted O_2 consumption at maximal heart rate (220 − age) and is expressed in the results on a per unit body weight basis. The volunteers wore the heart-rate monitor (Polar Sports Tester; Polar Electro, Kempele, Finland) continuously during waking hours over the following 4 d. Heart-rate readings were directly downloaded into a computer via a serial interface and the individual calibration data were used to predict minute energy expenditure for each person. Sleeping energy expenditure was calculated as 95 % BMR (Goldberg *et al*. 1988), where this was derived from published prediction equations (James & Schofield, 1990). A physical activity level (PAL), which is total energy expenditure : BMR, was computed for each day and averaged over the 4 d period.

Repeated-measures sub-study

The first twenty-five subjects in the cohort were asked to re-attend the testing site for measurements on three further occasions over the following year. Twenty-two of the subjects completed the protocol. Three other subjects began this part of the study but dropped out; one became pregnant, one had a back injury and had to leave the study, and the third decided that she was too busy to attend. Volunteers attended at 4-month intervals and, on each occasion, measurements were taken of height, weight and impedance using the methods described previously. The calibration between heart rate and resting and exercise energy expenditure was performed as before and the volunteers then underwent 4 d heart-rate monitoring.

Analytical methods to compute reliability coefficient

The reliability coefficients ($\hat{\rho}$) for PAL, height, weight, BMI, percentage body fat and V_{O_2max} per kg were estimated

using the formulas described by Armstrong *et al*. (1994). By this method, each of n subjects is measured k times with X_{ij} being the jth measure of subject i; $\bar{x}_i$ is the mean of k measurements in subject i, and $\bar{x}$ is the overall mean. $\hat{\rho}$ is given by the formula below.

$$\hat{\rho} = R_1 = \hat{\sigma}_s^2 / \hat{\sigma}_x^2 = (\mathrm{BMS} - \mathrm{WMS}) / (\mathrm{BMS} + (k-1)\mathrm{WMS}),$$

where BMS is the between-subject mean square, i.e. between-subject sum of squares/df:

$$\mathrm{BMS} = k \sum_i (\bar{x}_i - \bar{x})^2 / (n-1),$$

and WMS is the within-subject mean square, i.e. within-subject sum of squares/df:

$$\mathrm{WMS} = \sum_i \sum_j (x_{ij} - \bar{x}_i)^2 / n(k-1).$$

Results

The subjects (n 164) aged 30–40 years underwent a 75 g oral glucose tolerance test. Two subjects were unable to complete the estimation of resting energy expenditure, so all analyses were conducted on the complete dataset of 162 individuals. Two subjects were found to have previously undiagnosed non-insulin-dependent diabetes mellitus by World Health Organization Study Group (1985) criteria and four had impaired glucose tolerance. Table 1 shows the features of the subjects classified according to the binary categorization of the metabolic cardiovascular syndrome as previously defined. Using this classification, twelve of the men (16·4 %) and sixteen women (18·0 %) were classified as having the syndrome. Men with the syndrome were more centrally obese, had a lower PAL and were less fit than those without the syndrome, although none of these differences were statistically significant. The women who displayed the metabolic characteristics of the syndrome were more obese ($P < 0{\cdot}05$) and less fit ($P < 0{\cdot}001$) than those classified as not having the syndrome (Table 1). The group of subjects with the syndrome had a higher 2 h plasma glucose concentration, lower HDL-cholesterol level, higher triacylglycerol level and higher diastolic blood pressure. They also had higher LDL-cholesterol level and an elevated fasting insulin, intact and 32,33 split proinsulin concentration (Table 2).

Table 1. Anthropometric fitness and energy expenditure features of the study population by binary category of metabolic cardiovascular syndrome (MCS) and sex (n 162)

(Mean values and standard deviations)

	Subject without features of MCS		Subjects with features of MCS	
	Mean	SD	Mean	SD
Men				
n	61		12	
Age (years)	36·1	2·8	36·9	3·1
BMI (kg/m^2)	26·9	4·9	27·9	3·0
Waist : hip ratio	0·917	0·07	0·940	0·04
Physical activity level†	1·92	0·40	1·73	0·35
V_{O_2max} per kg (ml O_2/min per kg)	37·7	8·1	33·9	5·2
Body fat (%)	21·2	5·7	21·8	4·2
Women				
n	73		16	
Age (years)	36·3	2·7	35·7	2·5
BMI (kg/m^2)	24·6	4·3	28·9*	7·3
Waist : hip ratio	0·773	0·05	0·802*	0·04
Physical activity level†	1·78	0·31	1·65	0·31
V_{O_2max} per kg (ml O_2/min per kg)	30·6	6·3	25·0***	4·8
Body fat (%)	30·8	6·1	35·7**	7·8

V_{O_2max}, maximum O_2 consumption.
Mean values were significantly different from those for subjects without features of MCS: *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.
† Total energy expenditure : BMR.

Subjects were classified into sex-specific quartiles for mean PAL (Table 3) on the basis of the results from the 4 d heart-rate monitoring. The association between PAL quartile and metabolic cardiovascular syndrome was computed by calculating the odds ratio using the lowest PAL quartile as the reference category. The unadjusted odds ratios treating PAL quartile as a categorical variable are shown in Table 3. The overall association treating PAL quartile as an ordered categorical variable was 0·64 (95 % CI 0·43–0·94). This association is independent of obesity and sex, as in logistic regression analysis with the binary category of the metabolic cardiovascular syndrome as the outcome variable, the odds ratio per quartile was 0·62. Thus, for each increasing quartile of PAL, the risk of having metabolic cardiovascular syndrome independent of any effect of obesity was decreased by 38 %. There was also a strong association between cardio-respiratory fitness, as measured by V_{O_2max} per kg, and the metabolic cardiovascular syndrome (Table 4). The overall association per increasing sex-specific quartile of V_{O_2max} per kg was 0·49 (95 % CI 0·32–0·74), with the lowest quartile as the reference category.

$\hat{\rho}$ for the anthropometric measures, V_{O_2max} per kg and PAL estimates for the twenty-two subjects in the repeated-measures sub-study are shown in Table 5. Weight, height, BMI and percentage body fat all had high $\hat{\rho}$ values. Thus, a single estimate of these indices in an epidemiological study is likely to be an accurate estimate of the usual level. This is a reflection not only of the precision of the measurement but also of the inherent biological stability of the true value. By contrast, a single estimate of V_{O_2max} per kg by the method employed in the present study was only a moderately precise measure of usual fitness. Since usual energy expenditure is inherently more variable across 1 year, a single estimate of PAL was a relatively poor estimator of the habitual level. This variability is shown in Fig. 1, which plots the mean of the PAL estimates at 0, 4 and 8 months *v.* the independent measure at 12 months in the twenty-two subjects.

The data from the repeated-measures study were used to adjust the observed association for measurement error (Table 6). Using the attenuation formula, the true odds ratio was computed as 0·32 per quartile for PAL and 0·44 per quartile for V_{O_2max} per kg; i.e., the observation that per quartile the crude association, as judged by the unadjusted odds ratio, was stronger for V_{O_2max} per kg than for PAL, would be reversed if the measurement error were taken into consideration. When the same computations were undertaken with PAL entered into the model as a continuous variable, the unadjusted odds ratio per 0·1 increase in PAL was 0·86 (95 % CI 0·33–0·98). Adjustment for sex,

Table 2. Characteristics of subjects with and without features of metabolic cardiovascular syndrome (MCS; *n* 162)

(Mean values and standard deviations for normally distributed variables and geometric means and 95 % CI for skewed variables which were normalized by logarithmic transformation)

	Subject without features of the MCS			Subjects with features of the MCS		
	Mean	SD	95 % CI	Mean	SD	95 % CI
Men						
n	61			12		
Fasting plasma glucose (mmol/l)	4·89	0·4		5·30*	0·9	
2 h plasma glucose (mmol/l)	4·80	1·0		6·30	3·4	
LDL-cholesterol (mmol/l)	3·49	0·9		4·00	1·2	
HDL-cholesterol (mmol/l)	1·35	0·3		1·06**	0·3	
Triacylglycerol (mmol/l)	1·06		0·95–1·19	2·25***		1·90–2·66
Systolic blood pressure (mm Hg)	122·4	12·2		139·4***	18·2	
Diastolic blood pressure (mm Hg)	75·5	9·3		86·2***	13·1	
Fasting insulin (pmol/l)	40·2		34·1–47·5	59·0**		48·4–72·0
Fasting intact proinsulin (pmol/l)	5·15		4·5–6·0	7·61*		5·9–9·8
Fasting 32, 33 split proinsulin (pmol/l)	6·60		5·6–7·8	10·2*		7·7–13·4
Women						
n	73			16		
Fasting plasma glucose (mmol/l)	4·55	0·4		4·89	0·8	
2 h plasma glucose (mmol/l)	4·93	1·1		6·34*	2·4	
LDL-cholesterol (mmol/l)	3·16	0·9		3·30	0·9	
HDL-cholesterol (mmol/l)	1·72	0·4		1·19***	0·3	
Triacylglycerol (mmol/l)	0·84		0·76–0·92	1·27***		0·93–1·74
Systolic blood pressure (mm Hg)	115·1	9·5		120·6	17·2	
Diastolic blood pressure (mm Hg)	71·0	7·9		74·3	12·5	
Fasting insulin (pmol/l)	32·3		28·6–36·4	47·6*		35·2–64·4
Fasting intact proinsulin (pmol/l)	3·37		3·1–3·7	4·38*		3·3–5·9
Fasting 32, 33 split proinsulin (pmol/l)	4·12		3·7–4·6	6·20**		4·9–7·8

Mean values were significantly different from those for subjects without features of MCS: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

obesity and measurement error reduced the odds ratio to 0·67 (95 % CI 0·06–0·95).

Discussion

The values for $\hat{\rho}$ calculated in the present study demonstrate the variation in the extent to which single measures of certain biological variables reflect the usual or habitual level. As it is the latter which is usually the exposure of interest in epidemiological studies, knowledge of the differences in the reliability of single estimates of these variables is fundamental to the interpretation of observed associations. A single measurement of height is an excellent measure of usual height, not only because the measurement of height is relatively precise, but because this is an inherently stable biological phenomenon. By contrast, cardio-respiratory fitness, as measured by the V_{O_2max} per kg, is subject to variation, not only because it is more difficult to measure than height, but also because the true value (usual fitness) that is being estimated is more variable. The lowest $\hat{\rho}$ was observed for PAL. However, this does not imply that the measurement instrument is inadequate. The physiological variable that is being assessed by PAL is inherently more variable than any of the other variables that were considered in the present study. The low level of $\hat{\rho}$ means that the true association between a disease outcome and true

Table 3. Univariate unadjusted association between physical activity level (total energy expenditure:BMR; PAL) quartile and the binary classification of the metabolic cardiovascular syndrome (MCS; *n* 162)*

	No. of subjects		MCS	
PAL quartile†	MCS	Normal	Odds ratio	95 % CI
1‡	12	28	1	
2	7	33	0·49	(0·14–1·60)
3	4	38	0·25	(0·05–0·94)
4	5	35	0·33	(0·08–1·18)

* For details of subjects and classification of MCS, see Tables 1 and 2 and pp. 236–238.
† PAL quartiles:
Men < 1·615, 1·615–1·825, 1·825–2·050, > 2·050;
Women < 1·518, 1·518–1·761, 1·761–1·958, > 1·958.
‡ Reference category for calculation of odds ratio.

Table 4. Univariate unadjusted association between maximum oxygen consumption (V_{O_2max}) per kg and the binary classification of the metabolic cardiovascular syndrome (MCS; *n* 162)*

	No. of subjects		MCS	
V_{O_2max} per kg quartile†	MCS	Normal	Odds ratio	95 % CI
1‡	12	27	1	
2	9	31	0·65	(0·21–2·00)
3	6	38	0·36	(0·10–1·19)
4	1	38	0·06	(0·01–0·46)

* For details of subjects and classification of MCS, see Tables 1 and 2 and pp. 236–238.
† V_{O_2max} per kg quartile:
Men < 32, 32–35·8, 35·8–42, > 42;
Women < 25, 25–29·6, 29·6–34·5, > 34·5.

Table 5. Reliability coefficients for anthropometric, fitness and energy expenditure measurements for repeated-measures sub-study of twenty-two subjects*

	Within-subject mean square	Between-subject mean square	Reliability coefficient	Validity coefficient
Weight (kg)	5·638	2286	0·990	0·995
Height (m)	0·134	251·8	0·998	0·999
BMI (kg/m^2)	0·641	189·8	0·987	0·993
Percentage body fat	2·757	327·5	0·967	0·983
V_{O_2max} per kg (ml O_2/min per kg)	22·93	310·7	0·758	0·871
Physical activity level†	0·067	0·261	0·420	0·648

V_{O_2max}, maximum O_2 consumption.
* For details of subjects and procedures, see pp. 236–238.
† Total energy expenditure : BMR.

habitual energy expenditure would be markedly attenuated if the latter was assessed by a single 4 d measurement of PAL.

In the study presented here, the unadjusted relationship between fitness, as measured by a single estimate of V_{O_2max} per kg, and the metabolic cardiovascular syndrome was stronger than that for total energy expenditure, as measured by PAL. If the measurement error in the exposure were not taken into account, it might appear logical to conclude that V_{O_2max} per kg was a more important determinant of this syndrome than PAL. However, when the measurement error is included, this conclusion is reversed, as the adjusted association is stronger for PAL. These findings suggest that total energy expenditure is a major determinant of the risk of having this syndrome. However, cross-sectional data cannot prove causality, and evidence from prospective cohort and intervention studies would be required to make stronger causal inferences.

Comparing the present study with previously published reports is complicated by the heterogeneity of types of physical activity assessment instrument used in previous studies, and by associations which are described with the components of the syndrome rather than with the metabolic cardiovascular syndrome as a whole. If glucose tolerance is taken as an example, an association with physical activity is supported by evidence from seven prospective epidemiological studies (Helmrich *et al*. 1991; Manson *et al*. 1991, 1992; Burchfiel *et al*. 1995; Perry *et al*. 1995; Lynch *et al*. 1996; Haapanen *et al*. 1997). None of these studies use a method for assessing physical activity which is able to quantify total energy expenditure. For example, two of the studies used a single question on self-reported frequency of sweat-inducing vigorous activity (Manson *et al*. 1991, 1992), the British Regional Heart Study (Perry *et al*. 1995) used a physical activity score in six levels and the University of Pennsylvania Alumni Study (Helmrich *et al*. 1991) a questionnaire mainly consisting of self-reported participation in sports and recreations. Although these methods are sufficient to demonstrate associations, they do not provide evidence about which aspect of physical activity is of most benefit. The Health Professionals question (Manson *et al*. 1991, 1992), for example, is more likely to be assessing fitness rather than total energy expenditure, as previous comparison studies have shown a relationship with V_{O_2max} (Siconolfi *et al*. 1985). The Paffenbarger questionnaire, as used in the University of Pennsylvania Alumni Study (Helmrich *et al*. 1991), also has a closer relationship to fitness than it does to energy expenditure (Wareham *et al*. 1997). However, the true exposure that is being assessed is often not discussed in papers using this questionnaire, and terms like fitness, activity and energy expenditure are used interchangeably.

The lack of clarity in physical activity epidemiology is a hinderance to the development of appropriate public health interventions. Heart-rate monitoring has a clearly defined relationship to the true exposure of interest as measured by physiological gold standard techniques, and can be applied within a population to measure habitual energy expenditure. The introduction of this method provides the opportunity to define and quantify exposure–disease relationships. Using the data from the present study, we would predict that the effect of

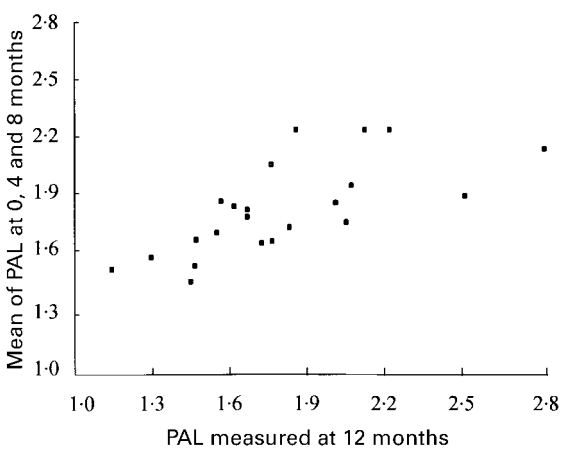

Fig. 1. Mean of three independent measures of physical activity level (total energy expenditure : BMR; PAL; 0, 4 and 8 months) *v.* PAL measured at month 12 in the repeated-measures sub-study of twenty-two subjects. For details of subjects and procedures, see pp. 236–238.

Table 6. Effect on observed odds ratio (OR) between physical activity level (PAL) and maximum oxygen consumption (V_{O_2max}) per kg and the metabolic cardiovascular syndrome of adjusting for BMI and the measurement error in the exposure of interest using data from the repeated-measures sub-study of twenty-two subjects*

	PAL†	V_{O_2max} per kg
Unadjusted OR per quartile	0·64	0·49
95% CI	(0·43–0·94)	(0·32–0·74)
OR per quartile adjusted for sex and BMI	0·62	0·54
95% CI	(0·42–0·92)	(0·34–0·83)
OR per quartile adjusted for sex, BMI and measurement error in exposure	0·32	0·44
95% CI	(0·13–0·83)	(0·24–0·78)

* For details of subjects and procedures, see pp. 236–238.
† Total energy expenditure : BMR.

a 0·1 increase in usual PAL would be to reduce the risk of the metabolic cardiovascular syndrome by 33 %. This degree of change in energy expenditure in a population could be achieved, for example, by the equivalent of an additional 4 h walking per week or just over 30 min daily. This type of quantitative estimate of potential benefit may prove useful in planning and evaluating population-level interventions.

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