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## Genetic and Environmental Influences on Total-Body and Central Abdominal Fat: The Effect of Physical Activity in Female Twins

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**Background:** The increasing prevalence of obesity has focused attention on the contribution of physical activity and its interaction with predisposing genetic factors.

**Objective:** To examine 1) the relation between physical activity and total-body and central abdominal fat, independent of genetic and other environmental factors, and 2) the influence of physical activity in persons who are genetically susceptible to generalized or central adiposity.

**Design:** Cross-sectional study.

**Setting:** A London academic teaching hospital.

**Patients:** 970 healthy female twins (mean age, 55.5 years [range, 39 to 70 years]; body mass index, 24.4 kg/m<sup>2</sup> [range, 16.4 to 44.0 kg/mg<sup>2</sup>]). There were 241 monozygotic pairs, 228 dizygotic pairs, and 32 women whose co-twin lacked complete data. Fifty-six percent of participants were of normal weight, 30% were overweight, 7% were obese, and 7% were underweight.

**Measurements:** Total-body and central abdominal fat were measured by dual-energy x-ray absorptiometry. Physical activity was assessed by quantitative and semi-quantitative questionnaires. Data on dietary intake, socioeconomic status, smoking status, and use of hormone replacement therapy (HRT) were also gathered.

**Results:** Total-body and abdominal central adiposity were lower with higher levels of home, sporting, and sweating-associated activity. Total-body and central abdominal fat were 5.6 kg and 0.44 kg lower, respectively, in participants who reported vigorous weight-bearing activity. Physical activity was the strongest independent predictor of total-body fat ( $\beta = -0.6$  [CI,  $-1.06$  to  $-0.15$ ];  $P = 0.009$ ) and central abdominal fat ( $\beta = -0.07$  [CI,  $-0.1$  to  $-0.03$ ];  $P < 0.001$ ) in a regression model that included age, diet, smoking, HRT use, and socioeconomic status. Monozygotic twin pairs who were concordant for smoking and HRT status but were discordant for moderate-intensity sport showed greater within-pair differences in total-body fat than those who were concordant for activity level. In this model, 1 and 2 hours of moderate-intensity sport accounted for within-pair differences of 1.0 kg ( $P = 0.050$ ) and 1.4 kg ( $P = 0.040$ ), respectively, of total-body fat. In participants who had an overweight twin, higher levels of

physical activity were still associated with 3.96-kg lower total-body fat and 0.53-kg lower central abdominal fat.

**Conclusions:** Current physical activity predicts lower total-body and central abdominal adiposity in healthy middle-aged women. After controlling for genetic and environmental factors, the influence of physical activity was greater than that of other measured environmental factors. Participants with a genetic predisposition to adiposity did not show a lesser effect of physical activity on body fat mass.

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Obesity is a major risk factor for type 2 diabetes mellitus, and both total-body and central abdominal obesity relate strongly to its precursor, insulin resistance (1, 2). Central abdominal adiposity predicts the development of type 2 diabetes and cardiovascular disease (3–7) and clusters with hypertension and dyslipidemia in syndrome X (8). Genetic factors influence both central abdominal obesity (9–11) and insulin resistance (12, 13), and it has been reported that genetic factors explain most of the population variance in total-body and central abdominal fat mass in healthy postmenopausal white women (9). Familial factors are also implicated in the reduction in central abdominal fat observed with intense physical training interventions in individual identical twins (14).

The increasing prevalence of overweight and obesity (15, 16) cannot, however, be explained by changes in the genetic makeup of populations but

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may be due to alterations in environmental factors (17). Population surveys link the increasing prevalence of overweight to markers of inactivity (17), and several reports suggest that higher levels of physical activity not only lessen total-body and central adiposity (18–22) but can prevent such sequelae as type 2 diabetes (23–25).

An interaction between environmental factors and genes regulating total-body and central abdominal fat mass that specifically favor obesity may be involved in the increasing prevalence of obesity and diabetes. The potential interaction between genetic susceptibility to generalized or central abdominal obesity and varied levels of physical activity has not yet been examined.

Data from twins provide a useful experimental model that can examine the direct effects of an environmental factor, such as physical activity, on total-body and central abdominal fat mass independent of genetic influences (the monozygotic co-twin case–control study) and can detect an interaction with predisposing genetic factors (gene–environment interaction). We studied a cohort of female twins to determine 1) the effect of physical activity on direct measures of total-body and central abdominal fat, independent of genetic and other environmental influences, and 2) whether similar amounts of physical activity have a lessened effect in persons who seem to be genetically predisposed to adiposity compared with those who are not.

## Methods

Participants ( $n = 970$ ) were white female twins identified from PHENOBASE (Gemini Holdings, Cambridge, United Kingdom), a database that includes intermediate phenotype and genetic information on unselected twin pairs. The twins in this study were recruited from a national media campaign to participate in wide-ranging studies at St. Thomas' Hospital in London (26). Zygosity was determined by a standardized questionnaire of similarity (27) and was confirmed by multiplex DNA fingerprinting with the AmpFL STR Profiler polymerase chain reaction kit (PE Applied Biosystems, Foster City, California). There were 241 monozygotic pairs, 228 dizygotic pairs, and 32 participants whose co-twin lacked complete data. These latter participants were included in the cross-sectional analysis only. All participants gave informed consent, and the study was approved by the local research and ethics committee. Volunteers were unaware of any hypotheses regarding body fat.

Pairs were assessed on the same day. Weight and height were measured while participants were barefoot and wearing light street clothes; weight was

rounded to the nearest one tenth of a kilogram and height was rounded to the nearest centimeter. Body mass index (weight in kg/height in  $m^2$ ) was used to confirm the population distribution of weight in this normal healthy group. Healthy weight was defined as 20.0 to 24.9  $kg/m^2$ , overweight was defined as 25.0 to 29.9  $kg/m^2$ , obese was defined as 30.0  $kg/m^2$  or more, and underweight was defined as 19.9  $kg/m^2$  or less. Body composition was measured by using dual-energy x-ray absorptiometry (Hologic QDR, Waltham, Massachusetts). Total-body fat (mass and percentage of body weight) was determined by using the standard software calculation. Central abdominal fat was measured by a single blinded investigator and was defined as the abdominal region extending from the top of the second lumbar to the bottom of the fourth lumbar vertebrae and laterally to the inner aspect of the ribs (9); this region relates strongly to central abdominal fat as measured by computed tomography (28, 29) and to insulin resistance as measured by euglycemic hyperinsulinemic clamping (2). Central abdominal fat is expressed as mass of fat tissue in the defined region (in kg) and as a percentage of the regional mass.

Physical activity was assessed with two standardized questionnaires administered by trained research nurses. Questionnaire 1 (used for 681 participants) assessed overall current physical activity in three situations—at home or work, in sport, and in walking—and included a four-point assessment of the intensity of activity (30). Scores were derived as follows: home or work activity, 1 = sedentary, 2 = sedentary with occasional exercise, 3 = half sedentary and half active, and 4 = active all day; weekly sporting activity, 1 = none, 2 = 1 hour of medium-intensity sport, 3 = 2 hours of medium-intensity sport or 1 hour of strenuous sport, and 4 = 2 hours of strenuous sport; and weekly walking activity, 1 = less than half a mile, 2 = 0.5 to 5 miles, 3 = 5.5 to 10 miles, and 4 = more than 10 miles. Examples of medium-intensity sports included golf, bowling, cycling, or swimming; strenuous sports included aerobics or squash. The maximum total activity score possible was 12. Participants were also asked whether they participated in weekly physical activity of an intensity that produced sweating; this question was adapted from the questionnaire of Paffenbarger and colleagues (31).

Questionnaire 2, which was based on the Allied Dunbar National Fitness Survey (32), assessed leisure activity in detail. Participants ( $n = 804$ ) reported whether they currently participated in leisure-time physical activity regularly and quantified the time they spent (in 15-minute units) engaging in weight-bearing and non-weight-bearing sports of moderate and vigorous intensity. Multiple examples

were given for each category of activity. A total of 516 participants answered both questionnaires.

Quadriceps muscle strength was measured by using the Leg Extensor Power Rig (Medical Physics Department, Queens Medical Centre, Nottingham, United Kingdom), which estimates physical function (in watts), relates well to physical performance (33), and provides a measure of muscle strength not confounded by balance in middle-aged and elderly persons. After practice, quadriceps strength was measured three times and the best effort was recorded.

Dietary intake was measured in a subgroup of participants ( $n = 355$ ) by using a food-frequency questionnaire (34), which has been described elsewhere (35). This questionnaire has been validated in a similarly aged population by using 16-day weighed records and biological markers (34, 36). Energy underreporters were defined as participants whose estimated basal energy expenditure exceeded their reported energy intake. Basal energy expenditure was calculated by using the formula of Garby and associates (37), and fat mass and fat-free mass were measured by using dual-energy x-ray absorptiometry scanning; details of these methods can be found elsewhere (35). Energy underreporters were excluded from subsequent analyses involving dietary measures. Socioeconomic class was determined by the standardized method for the United Kingdom according to the subject's or her partner's occupation. There were six categories: professional I (such professions as physician, lawyer, academician, or pharmacist); professional II (such professions as teacher, nurse, computing, or managerial); IIIa, skilled nonmanual work; IIIb, skilled manual work; IV, unskilled manual work; and V, cleaning or labor. Smoking habit, menopausal status, and use of postmenopausal hormone replacement therapy (HRT) were also ascertained by standardized questionnaire.

## Statistical Analyses

### *Cross-Sectional Analyses*

Cross-sectional relations between body fat and physical activity were first examined by using simple regression analysis and analysis of variance. For simple regressions, the slope and 95% CIs are presented. Characteristics in twins are not independently determined because of common genetic and environmental influences. Owing to the similarity within twin pairs, standard errors may be underestimated and, consequently,  $P$  values may be overstated, unless the correlation between twins is accounted for. To correct for this similarity in the cross-sectional analyses of the entire cohort, the generalized estimating equation modeling approach was used to determine the linear association between variables (38). This approach accounts for the correlation

within twin pairs and yields consistent estimates of linear association terms and their corresponding SEs. Its application to cross-sectional correlated observations is reported elsewhere (39, 40). All dizygotic twin pairs, the 32 participants for whom co-twin data were missing, and one woman from each monozygotic twin pair (randomly selected) were included in generalized estimating equation analyses. Where analysis of variance was performed to compare two groups, the  $F$ -test was used as a global test for group mean differences within the generalized estimating equation models.

It was previously shown (41) that smoking, HRT use, and dietary sugar intake (35) influence adiposity in this cohort. These factors were included in a multiple regression model in addition to socioeconomic status to estimate the influence of physical activity independent of these covariates. Although no relation was found between energy and dietary fat intake and adiposity in this cohort (35), additional regression models were constructed that included physical activity, energy and dietary fat intake, smoking, HRT use, and socioeconomic status.

In all of our models, normality and homogeneity of variance assumptions were satisfied. The main and first-order interaction terms were tested in all regression models reported, except for variables with categorical scores for which fitting the full first-order interaction model was degenerate.

### *Monozygotic Twin Analyses (Co-Twin Case-Control Study)*

The discordant monozygotic twin-pair model (also called the co-twin case-control study design) is a powerful tool for specifically investigating the relation between two variables in two genetically identical persons: (35, 41–43). This model has been used to determine the influence of HRT use, smoking, and dietary intake on fat mass (35, 41), the influence of smoking on bone density (42), and the relation between body fat and leptin levels (43). Because monozygotic twins share approximately 100% of their genes, differences in body fat within a pair must result from environmental differences. This model was used to estimate the influence of various aspects of physical activity, isolated from genetic and other environmental influences. Only monozygotic twin pairs who were concordant for HRT use and smoking status were included in these analyses (156 pairs) and were classified as concordant or discordant for physical activity on the basis of reported degrees of walking, home or work activity, sporting activity, and sweating-associated activity from questionnaire 1. Within-pair differences in body fat in monozygotic twin pairs who were concordant and those who were discordant for degrees of activity were compared by using analysis of vari-

ance (41) to estimate the influence of activity. Monozygotic twin pairs who were discordant for total activity were further analyzed by using paired *t*-tests to determine whether higher activity within the pair was associated with higher or lower total-body fat. In an additional analysis controlling for energy intake, only monozygotic twin pairs concordant for tertile of energy intake, smoking status, and HRT use were included. Because dietary data were available only in a subgroup of twins, only 40 twin pairs were included in this analysis.

### Gene-Environment Interaction Analyses

The twin model enabled us to examine whether physical activity has a smaller effect in persons who were genetically predisposed to obesity (gene-environment interaction) by using methods described elsewhere (44, 45). The question to be examined is whether participants who are genetically predisposed to obesity show a differential effect of physical activity on fat mass. Given the strong genetic influence on fat mass in this cohort (9) and in the absence of validated susceptibility loci or genes, the phenotype of a twin's co-twin can be used as a marker of underlying genetic risk (45). That is, if a twin's co-twin is overweight, it can be assumed that the twin also has a higher genetic risk for being overweight.

The data were then analyzed as follows. The degree of genetic risk for obesity was defined by using tertiles of body fat for the whole cohort; the highest tertile was 27.8 to 65.0 kg of body fat and the lowest was 6.8 to 21.3 kg of body fat. Within each twin pair, twin 1 was assigned a category of genetic risk on the basis of the body fat tertile of her co-twin; twin 1 had a high genetic risk if her co-twin was in the highest body fat tertile and a low genetic risk if her co-twin was in the lowest body fat tertile. Both monozygotic and dizygotic twin pairs were included in these analyses; all were concordant for smoking and HRT status. Analyses were performed by using both twins from each pair and only one (randomly chosen) from each pair. The latter analyses were undertaken to minimize the chance that within-pair similarity would inflate the significance of the result. Results were similar from both approaches, and only the analyses using one twin from each pair are presented. Sixty-seven twins had a low genetic risk for being overweight and 69 twins had a high genetic risk. Physical activity was categorized into high and low activity by using the score from questionnaire 1 (highest activity score = 9 [ $n = 68$ ]; lowest activity score = 6 [ $n = 68$ ]). We tested for an interaction between genetic risk category and physical activity category by using a two-factor analysis of variance that assessed multiplicative effects of genetic risk category and physical

activity level. This method was repeated with central abdominal obesity against activity level. Genetic risk for central abdominal adiposity for twin 1 was defined by the central abdominal fat value of her co-twin using tertile measures for central abdominal fat mass; the highest-risk tertile was 1.77 to 4.60 kg and the lowest-risk tertile was 0.08 to 1.18 kg.

Data are presented as the mean ( $\pm$  SE), except where otherwise stated. Simple and multiple regression analyses, one-way analysis of variance, two-factor analysis of variance, and paired *t*-tests were performed by using StatView SE + Graphics (Abacus Concepts, Inc., Berkeley, California). Generalized estimating equations were calculated by using Stata software (Stata Corp., College Station, Texas). All tests were two-sided.

### Role of the Funding Source

The funding sources had no role in the collection, analysis, or interpretation of data or the decision to submit the study for publication.

## Results

The mean age ( $\pm$ SD) in 970 participants was  $55.5 \pm 7.7$  years (range, 39 to 70 years); their mean body mass index was  $24.4 \pm 3.8$  kg/m<sup>2</sup> (range, 16.4 to 44.0 kg/mg<sup>2</sup>). Body composition and quadriceps muscle extensor strength are shown in **Table 1**. Fifty-six percent of the cohort were of normal weight, 30% were overweight, 7% were obese, and 7% were underweight. Age was related to both the percentage of total-body fat ( $\beta = 0.17$  [CI, 0.09 to 0.25];  $r^2 = 0.03$ ;  $P < 0.001$ ) and percentage of central abdominal fat ( $\beta = 0.23$  [CI, 0.09 to 0.37];  $r^2 = 0.02$ ;  $P = 0.001$ ). Quadriceps muscle extensor strength did not relate to body mass index, total-body fat, or central abdominal fat (data not shown).

### Cross-Sectional Analyses

#### Questionnaire 1: Total Physical Activity and Activity Subtypes

Total physical activity was composed of scores for home or work activity, walking, and sporting activity. Home or work activity related to sporting activity ( $r = 0.25$ ;  $P < 0.001$ ) and walking activity ( $r = 0.30$ ;  $P < 0.001$ ); however, walking activity did not relate to sporting activity ( $r = 0.07$ ;  $P = 0.06$ ). Participants who reported higher activity scores in each category of activity ( $n = 681$ ) had lower body mass index and total-body fat values (**Table 1**). Only participants who reported higher activity scores in home or work activity and sporting activity had lower central abdominal fat values (**Table 1**). Mus-

**Table 1. Total-Body and Central Abdominal Fat According to Home or Work Activity, Sporting Activity, and Walking in Middle-Aged British Women\***

Activity Type	Body Mass Index	Total Fat Mass	Total Fat	Central Fat Mass	Central Fat	Fat-Free Mass	Muscle Strength
	kg/m <sup>2</sup>	kg	%	kg	%	kg	W
Mean value (± SD)	24.4 ± 3.8	25.4 ± 8.3	38.6 ± 7.5	1.55 ± 0.70	36.5 ± 10.3	37.4 ± 4.7	82.4 ± 33.7
Home or work activity							
Category 1 (n = 17)	24.9 ± 1.1	25.4 ± 2.6	37.6 ± 2.2	1.49 ± 0.28	33.5 ± 4.3	41.0 ± 2.6	77.1 ± 9.7
Category 2 (n = 113)	25.8 ± 0.4	27.9 ± 0.9	40.4 ± 0.7	1.78 ± 0.09	38.7 ± 1.0	37.9 ± 0.6	79.5 ± 3.8
Category 3 (n = 350)	24.5 ± 0.2†	25.7 ± 0.4†	39.1 ± 0.4	1.55 ± 0.04†	36.8 ± 0.6	37.0 ± 0.3‡	80.9 ± 2.1
Category 4 (n = 224)	23.6 ± 0.2§	23.6 ± 0.5§	37.1 ± 0.5§	1.42 ± 0.06§	34.7 ± 0.9§	37.0 ± 0.4¶	86.3 ± 2.5
Sporting activity							
Category 1 (n = 399)	24.6 ± 0.2	26.3 ± 0.4	39.8 ± 0.4	1.64 ± 0.04	38.0 ± 34.6	36.9 ± 0.3	77.4 ± 1.8
Category 2 (n = 77)	24.5 ± 0.5	25.5 ± 1.1	38.0 ± 0.9**	1.50 ± 0.11	34.6 ± 1.5**	38.6 ± 0.8**	83.5 ± 4.1
Category 3 (n = 123)	24.4 ± 0.3	26.0 ± 0.7	39.6 ± 0.7‡	1.56 ± 0.07	37.1 ± 1.2	37.7 ± 0.6	92.9 ± 3.5‡
Category 4 (n = 63)	23.2 ± 0.4§¶	22.0 ± 0.9§¶	35.3 ± 1.0¶	1.14 ± 0.08§¶	30.1 ± 1.7§¶	36.9 ± 0.7	97.0 ± 4.9§¶
Walking							
Category 1 (n = 23)	24.4 ± 0.8	25.7 ± 1.7	39.3 ± 1.5	1.77 ± 0.19	39.3 ± 2.8	37.1 ± 1.3	84.8 ± 9.8
Category 2 (n = 327)	24.9 ± 0.2	26.4 ± 0.5	39.8 ± 0.4	1.59 ± 0.05	37.1 ± 0.7	37.1 ± 0.3	78.3 ± 2.1
Category 3 (n = 216)	24.1 ± 0.2†	24.9 ± 0.6	38.0 ± 0.5†	1.55 ± 0.06	36.3 ± 0.9	37.3 ± 0.4	88.5 ± 2.6†
Category 4 (n = 138)	23.7 ± 0.3§	23.5 ± 0.7†	36.8 ± 0.6§	1.42 ± 0.06	34.8 ± 1.0	37.4 ± 0.5	82.8 ± 3.5

\* All results are given as the mean ± SE, unless stated otherwise. Categories of physical activity were as follows: Home or work: 1 = sedentary, 2 = sedentary with occasional exercise, 3 = half sedentary-half active, 4 = active all day; weekly sporting activity: 1 = none, 2 = 1 hour of medium-intensity activity, 3 = 2 hours of medium-intensity activity or 1 hour of strenuous activity, 4 = 2 hours of strenuous activity; weekly walking activity: 1 = less than half a mile, 2 = 0.5 to 5 miles, 3 = 5.5 to 10 miles, 4 = more than 10 miles.

†  $P < 0.05$  for category 2 compared with category 3.

‡  $P < 0.05$  for category 1 compared with category 3.

§  $P < 0.05$  for category 2 compared with category 4.

||  $P < 0.05$  for category 3 compared with category 4.

¶  $P < 0.05$  for category 1 compared with category 4.

\*\*  $P < 0.05$  for category 1 compared with category 2.

cle strength was greater in participants who reported higher activity scores (Table 1).

Compared with participants who did not engage in sweating-associated activity, participants who reported sweating-associated activity at least weekly (31%) had lower total-body fat mass ( $24.1 \pm 0.6$  kg and  $26.0 \pm 0.4$  kg;  $P = 0.03$ ), lower total-body adiposity ( $36.8\% \pm 7.8\%$  and  $39.6\% \pm 0.3\%$ ;  $P = 0.001$ ), lower central abdominal fat mass ( $1.40 \pm 0.05$  kg and  $1.61 \pm 0.05$  kg;  $P = 0.010$ ), lower central abdominal adiposity ( $33.5\% \pm 0.9\%$  and  $37.7\% \pm 0.5\%$ ;  $P = 0.001$ ), greater lean tissue mass ( $39.0 \pm 0.4$  kg and  $36.8 \pm 0.3$  kg;  $P < 0.001$ ), and greater muscle strength ( $93.5 \pm 2.6$  W and  $77.5 \pm 1.7$  W;  $P < 0.001$ ). The age of the two groups was similar ( $56.0 \pm 0.5$  years and  $56.8 \pm 0.3$  years, respectively;  $P = 0.14$ ).

In tertile analysis of total activity levels, total-body fat was significantly greater in participants in the lowest tertile ( $26.6 \pm 0.6$  kg) than in those in the middle ( $25.2 \pm 0.5$  kg) and highest ( $23.9 \pm 0.5$  kg) tertiles ( $P = 0.002$ ). Similarly, central abdominal fat was significantly greater in participants in the lowest total activity tertile ( $1.66 \pm 0.06$  kg) than in those in the middle ( $1.55 \pm 0.05$  kg) and highest ( $1.38 \pm 0.06$  kg) tertiles ( $P = 0.003$ ). Muscle strength was greatest in the highest tertile of physical activity ( $90.2 \pm 2.7$  W) compared with the lowest ( $76.5 \pm 2.6$  W) and middle ( $81.4 \pm 2.3$  W) tertiles ( $P = 0.01$ ); this result is consistent with self-reported activity.

After energy underreporters were excluded, in participants with validated dietary data (35) ( $n = 355$ ), the independent influence of physical activity

level on total-body and central abdominal fat was examined in a multivariate model that included age, smoking status, socioeconomic class, HRT use, and dietary intake of simple carbohydrates. Physical activity level was consistently the strongest independent predictor of total-body fat mass ( $\beta = -0.60$  [CI,  $-1.06$  to  $-0.15$ ];  $P = 0.009$ ) and central abdominal fat mass ( $\beta = -0.07$  [CI,  $-0.10$  to  $-0.03$ ];  $P < 0.001$ ). In these analyses, the only other significant predictor of total-body fat mass was carbohydrate intake ( $\beta = -0.18$  [CI,  $-0.185$  to  $-0.177$ ];  $P = 0.01$ ). Together, these two factors accounted for 44% of the variance in total-body fat mass. In a second model that included physical activity, age, smoking status, socioeconomic class, HRT use, and energy and dietary fat intake, physical activity was again the strongest independent predictor; dietary factors did not contribute significantly to the variance in total-body fat (data not shown).

### Questionnaire 2: Type and Intensity of Leisure-Time Activity

Age and body composition were similar for participants who responded to questionnaire 2 ( $n = 804$ ) and those who answered questionnaire 1 (data not shown). Compared with participants who considered themselves inactive, participants who classified themselves as physically active had lower body mass index ( $23.9 \pm 0.2$  kg/m<sup>2</sup> and  $24.7 \pm 0.2$  kg/m<sup>2</sup>;  $P = 0.004$ ), total-body fat mass ( $23.4 \pm 0.4$  kg and  $25.8 \pm 0.4$  kg;  $P < 0.001$ ), and central abdominal fat mass ( $1.40 \pm 0.04$  kg and  $1.66 \pm 0.04$  kg;  $P < 0.001$ )

**Table 2. Relation of Regular Leisure Activity to Total-Body and Central Abdominal Fat in Middle-Aged British Women\***

Characteristic	Moderate-Intensity Weight-Bearing Sport		Moderate-Intensity Non-Weight-Bearing Sport		Vigorous-Intensity Weight-Bearing Sport	
	Yes (n = 188)	No (n = 616)	Yes (n = 154)	No (n = 649)	Yes (n = 46)	No (n = 758)
Body mass index, kg/m <sup>2</sup>	23.5 ± 0.2	24.6 ± 0.2†	24.4 ± 0.31	24.4 ± 0.2	22.6 ± 0.4	24.5 ± 0.1†
Total fat mass, kg	22.8 ± 0.5	25.5 ± 0.3‡	24.4 ± 0.7	24.9 ± 0.3	19.6 ± 0.9	25.2 ± 0.3‡
Total fat, %	35.9 ± 0.6	38.5 ± 0.3‡	37.3 ± 8.0	38.0 ± 0.3	31.3 ± 1.0	38.3 ± 0.3‡
Central fat mass, kg	1.37 ± 0.05	1.61 ± 0.03†	1.46 ± 0.6	1.57 ± 0.03	1.14 ± 0.10	1.57 ± 0.29†
Central fat, %	34.1 ± 0.9	37.1 ± 0.4†	35.3 ± 0.9	36.5 ± 0.5	27.9 ± 2.0	36.7 ± 0.4‡
Muscle strength, W	96.0 ± 3.2	82.3 ± 1.7†	92.3 ± 3.3	84.2 ± 1.7	121.1 ± 5.9	83.6 ± 1.5‡

\* All values are given as the mean ± SE.

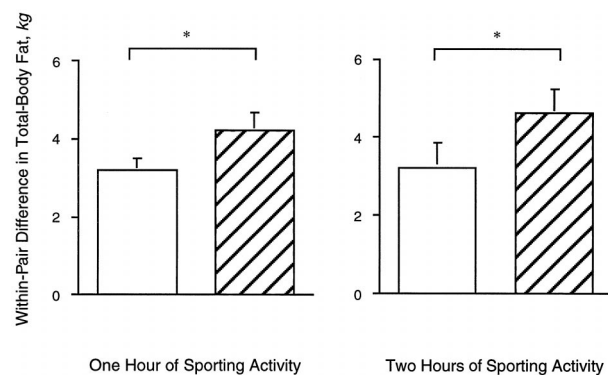
†  $P < 0.005$ .

‡  $P < 0.001$ .

and greater muscle strength ( $94.4 \pm 2.4$  W and  $80.0 \pm 1.9$  W;  $P < 0.001$ ).

All measures of body fat were consistently lower in participants who regularly performed moderate-intensity or vigorous weight-bearing activity; on average, total-body and central abdominal fat mass were 2.7 kg and 0.24 kg lower, respectively, among those who performed moderate-intensity weight-bearing activity and 5.6 kg and 0.43 kg lower, respectively, among those who performed vigorous weight-bearing activity (Table 2). Muscle strength was significantly greater in participants who performed moderate- or vigorous-intensity weight-bearing sporting activity (Table 2). Non-weight-bearing sport was not associated with significant differences in body fat variables (Table 2).

Among participants who performed moderate- or vigorous-intensity weight-bearing sport, the reported duration of activity per week did not relate to body fatness (data not shown), but trends for greater muscle strength were found with duration of moderate-intensity weight-bearing sport ( $\beta = 0.46$  [CI, 0.0 to 0.96];  $r^2 = 0.02$ ;  $P = 0.070$ ) and vigorous weight-bearing sport ( $\beta = 0.41$  [CI, 0.0 to 0.93];  $r^2 = 0.02$ ;  $P = 0.10$ ). No relation was found between body fatness or muscle strength and duration of non-weight-bearing sports (data not shown).



**Figure 1.** Within-pair differences in total-body fat in 156 monozygotic twin pairs who were concordant (white bars) or discordant (striped bars) for sporting activity. \*  $P \leq 0.05$ . Error bars represent upper bound of SE.

### Monozygotic Twin Analyses (Co-Twin Case-Control Study)

Among monozygotic twin pairs who were concordant for smoking status and HRT use ( $n = 156$  monozygotic pairs) and for whom the duration of moderate-intensity sporting activity differed by 1 hour per week, the difference in body fat mass was significantly greater than for pairs who were concordant for such activity ( $4.21 \pm 0.46$  kg and  $3.21 \pm 0.28$  kg;  $P = 0.05$ ) (Figure 1). With increasing discordance for moderate-intensity sporting activity, the within-pair differences in body fat mass were increasingly greater than in concordant pairs. For example, the within-pair difference in monozygotic pairs who were discordant for 2 hours of moderate-intensity sporting activity was  $4.60 \pm 0.63$  kg compared with  $3.23 \pm 0.63$  kg in concordant pairs ( $P = 0.04$ ) (Figure 1). After controlling for dietary intake by restricting the analyses to monozygotic pairs who were concordant for energy intake ( $n = 40$  pairs), the mean within-pair difference was  $5.42 \pm 1.5$  kg in monozygotic pairs who were discordant for 2 hours of moderate-intensity sporting activity and  $2.68 \pm 0.39$  kg in concordant pairs ( $P = 0.01$ ). Thus, a within-pair difference of 1 hour of moderate-intensity sporting activity accounted for a within-pair difference of approximately 1.0 kg of body fat. A within-pair difference of 2 hours of moderate-intensity sporting activity accounted for a within-pair difference of 1.4 kg of body fat (2.74 kg of body fat after controlling for energy intake). Discordance for home or work activity, walking, or sweating-associated activity was not associated with significantly different within-pair differences in total-body or central abdominal fat (data not shown).

Among all monozygotic twin pairs who were discordant for the total activity score ( $n = 164$  pairs), the twin with the higher activity levels had significantly lower total-body fat mass ( $24.50 \pm 0.57$  kg and  $26.01 \pm 0.68$  kg;  $P = 0.013$ ) and adiposity ( $38.1\% \pm 0.5\%$  and  $39.3\% \pm 0.6\%$ ;  $P < 0.001$ ) than the twin with lower activity levels. When only mono-

zygotic pairs concordant for smoking status and HRT use were included ( $n = 128$  pairs), similar results were found: The twin who did more exercise had lower total-body fat mass ( $24.14 \pm 0.61$  kg and  $25.49 \pm 0.68$  kg;  $P = 0.002$ ) and adiposity ( $37.1\% \pm 0.6\%$  and  $39.3\% \pm 0.6\%$ ;  $P < 0.001$ ).

### Gene–Environment Interactions

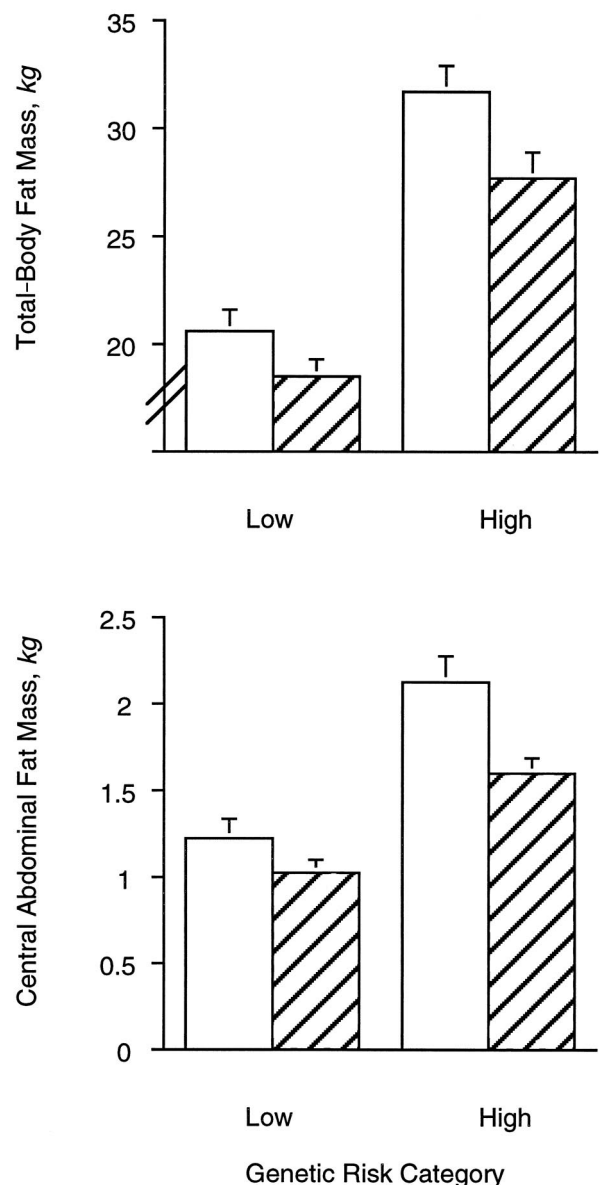
Data from monozygotic and dizygotic twin pairs were examined for a contributory gene–environment interaction in participants who were predisposed to obesity (that is, a lesser effect of physical activity). The data tended toward the contrary: The mean difference in total-body fat between high- and low-activity groups in participants with high genetic risk was greater (3.96 kg) than that between high- and low-activity groups in participants with low genetic risk (2.05 kg). Expressed as the difference over the mean, higher activity in the group with low genetic risk was associated with 10% lower total-body fat compared with 13% less total-body fat in the group with high genetic risk (two-factor analysis of variance not significant [ $P > 0.2$ ]).

Similarly, for central abdominal fat, the mean difference between high and low activity in the group with high genetic risk was 0.53 kg compared with 0.20 kg in the group with low genetic risk (Figure 2). Expressed as the difference over the mean, higher activity levels in the group with high genetic risk were associated with 27% lower central abdominal fat compared with 17% less central abdominal fat in the group with low genetic risk ( $P = 0.16$ ). Thus, the data do not support an interaction between genetic risk and physical activity that contributes to higher total-body or central abdominal fat mass in predisposed persons.

### Discussion

Physical activity is one environmental factor known to protect against and ameliorate obesity, a polygenic, multifactorial chronic disease, and its related conditions (21–25, 46–52). Despite recent advances, the cause of obesity in most patients remains unknown. We studied the influence of physical activity in approximately 1000 healthy female twin participants on total-body and central abdominal fat (measured by using direct methods). The study of twins permitted quantification of the influence of physical activity independent of genetic factors as well as testing for gene–environment interactions in persons with a genetic susceptibility to obesity.

Cross-sectional analyses confirmed an inverse relation between physical activity and total-body and central abdominal fat. The lowest total-body and



**Figure 2.** The influence of genetic risk and physical activity level on total-body fat mass (top) and central abdominal fat mass (bottom) in middle-aged female twins. White bars represent low physical activity; striped bars represent high physical activity. Error bars represent upper bound of SE.

central abdominal fat values were found in participants who were active at home or work or who performed 2 hours of sport, 10 miles of walking, or sweating-associated physical activity per week. In particular, weight-bearing sport of any intensity was related to lower total-body and central abdominal fat values and greater muscle strength. In the hierarchy of environmental factors influencing total-body and central abdominal fat, physical activity was strongest in a model that included dietary carbohydrate and fat, smoking, socioeconomic class, and HRT use. In analyses of monozygotic twins, all other measured environmental influences were controlled for: smoking status, HRT use, and diet. Twin

pairs who were discordant for moderate-intensity sporting activity had greater differences in total-body fat; the twin with the lower level of activity had higher body fat. Discordance for 2 hours of moderate-intensity activity accounted for 1.4 to 2.74 kg of total-body fat. There was no evidence of a gene-environment interaction between low-intensity physical activity and high genetic risk contributing to higher fat mass in genetically susceptible participants (those with an obese co-twin). Gene-environment interactions may be found, however, in larger populations or other ethnic groups or among prospective data.

The analyses of monozygotic twins seem to suggest a more limited influence of physical activity, after controlling for genetic and other environmental factors. This may be because there were fewer participants in these analyses; however, our estimate of the influence of physical activity on fat mass is not inconsistent with longitudinal studies estimating the influence of physical activity on body fatness (50-52). A meta-analysis of moderate exercise intervention in women found that moderate exercise was responsible for a loss of  $1.3 \pm 0.2$  kg body fat (50). One Australian study of a comparable cohort of women found that those who remained active after 5 years weighed 2 kg less than women who were inactive (51). Among Finnish women, those performing frequent leisure-time physical activity weighed 1.3 kg less than those who only rarely participated (52). In interventional or longitudinal studies, other unmeasured behavioral covariates may magnify the apparent effect of physical activity. A proportion of the apparent effects of physical activity found in cross-sectional or prospective studies may also be due to differences in genetic factors determining physical activity. Supporting evidence is increasing for this hypothesis: Genetic influences have been reported on physical activity level (53), weight change with physical activity (14, 54), and the capacity to exercise (muscle fiber type, hemodynamic responses, aerobic capacity, and muscle capillary density) (55, 56). Most recently, an angiotensin-converting enzyme polymorphism was associated with physical endurance (57); this may represent only one of many genes influencing the effect of physical activity.

Our findings support physical activity as a stronger determinant of total-body and central abdominal fat in middle-aged women than such environmental influences as reported dietary intake or smoking. By studying similar monozygotic twins, we found no relation between energy and fat intake and total-body or central abdominal fat mass (35). Weak inverse relations with simple carbohydrate and alcohol intake were found when validated measures of dietary intake were used and sources of bias, such as energy

underreporters, were excluded (35). In monozygotic twin pairs, differences in energy intake exceeding 480 kcal/d and differences in fat intake exceeding 10% of daily energy intake were not associated with any significant differences in total-body fat (35). Together with our current results, reported physical activity seems to be the strongest influence on total-body fat mass after genetic factors.

Several limitations of our study require consideration. Standard cross-sectional observational studies cannot distinguish the influence of activity discrete from other factors, such as genes (9) and environmental influences (35, 41). Although causality is usually established by prospective or interventional studies, it may be strongly inferred from cross-sectional twin data by using the monozygotic twin (co-twin case-control) model. This model represents a robust experiment in which age-matched, genetically and environmentally identical participants discordant for the environmental factor of interest are examined to isolate one environmental factor from other factors. Although they are not as predictive as a prospective study, monozygotic analyses have additional power over standard cross-sectional studies in that participants are genetically matched and no adjustment is required for potential confounders, such as age, sex, and known environmental factors.

One limitation of the monozygotic twin model is the assumption of identical genetic makeup. Monozygotic twins may have some genetic differences because of postzygotic somatic mutations or somatic recombinations (58); however, these contribute to within-pair differences in both concordant and discordant twin pairs (58). Current scientific methods cannot examine differences in genomic expression in populations as large as the one that we studied. In the current scientific paradigm, discordant monozygotic twin analysis represents a model of genetic similarity capable of testing the influence of environmental factors independent of genetic influences, with less potential for differences in genomic expression than that found in unrelated, cross-sectional populations.

Possible biases may exist, including activity overreporting, variable measurement error, and the possibility that lessened activity is a result of obesity. Because only a small proportion of participants were obese, the importance of such potential bias is lessened, particularly if overreporting occurs predominantly in obese persons as suggested (59). Although we did not assess activity overreporting, if it had been present in the obese participants, it would have underestimated the magnitude of the relation between physical activity and body fat. The use of the gold standard measure of energy expenditure, the doubly-labeled water technique, is limited in a study of this size by cost. Although differing mea-

surement errors in the self-reported physical activity and dietary questionnaires used may exist, the careful methods were intended to minimize such errors: We used direct measures of total-body and central abdominal fat and two physical activity questionnaires, and we excluded dietary energy under-reporters.

The question of whether obesity itself reduces physical activity is more difficult. Recent studies show that obese women achieve greater levels of oxygen consumption than lower-weight women while performing similar activities (60). These results suggest that obese participants achieve high exercise intensity when performing activities that are externally measured as low intensity. For example, obese women reach 70% of maximal aerobic capacity during walking on flat surfaces (60). The question of primacy of low activity or obesity can be determined by doing prospective studies; however, cross-sectional twin data and causation modeling can also be used, with confirmation from prospective observational twin studies.

In summary, we found that physical activity is the strongest environmental determinant of total-body and central abdominal fat mass in this population of healthy middle-aged women. After controlling for genetic and other environmental factors, the direct influence of moderate activity in this population seems modest, possibly because of direct genetic influences on activity levels. Of note, no contributory gene-environment interaction with physical activity in participants who were genetically susceptible to obesity was found; this implies that persons with a strong family history of obesity may not be disadvantaged in their response to increased physical activity, despite strong genetic factors regulating fat mass. Whether the influence of activity or genetic interaction (or both) is constant or varies at different stages of life has not been examined but could be determined by prospective studies in twin populations.

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