The Associations of Physical Activity and Adiposity with Alanine Aminotransferase and Gamma-Glutamyltransferase

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The mechanisms linking obesity and inactivity to diabetes mellitus are unclear. Recent studies have shown associations of alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) with diabetes. In a random sample of 3,789 British women aged 60–79 years, the authors examined the associations of obesity and physical activity with ALT and GGT (1999–2001). Both body mass index and waist:hip ratio were independently (of each other, physical activity, alcohol consumption, smoking, and childhood and adulthood social class) positively and linearly associated with ALT and GGT. In adjusted models, a one-standard-deviation increase in body mass index was associated with a 0.46-units/liter (95% confidence interval (CI): 0.16, 0.75) increase in ALT and a 2.14-units/liter (95% CI: 0.99, 3.30) increase in GGT. Similar results for a one-standard-deviation increase in waist:hip ratio were 13.96 (95% CI: 10.44, 17.48) for ALT and 39.44 (95% CI: 25.89, 52.98) for GGT. Frequency of physical activity was inversely and linearly associated with GGT in fully adjusted models, but the inverse association with ALT was attenuated towards the null after adjustment for body mass index and waist:hip ratio. Adjustment for ALT and GGT resulted in some attenuation of the strong linear associations of body mass index and waist:hip ratio with diabetes. These findings provide some support for the suggestion that the relation between obesity and diabetes is, at least in part, mediated by liver pathology.

alanine transaminase; body composition; body mass index; diabetes mellitus; exercise; gamma-glutamyltransferase; obesity; waist-hip ratio

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; GGT, gamma-glutamyltransferase.

Physical inactivity, greater body mass index, and central obesity are independent risk factors for the development of type 2 diabetes mellitus (1–5). Both moderate physical activity, including brisk walking, and more vigorous activity have been found to be associated with reduced risk of developing type 2 diabetes in women and men (6, 7). In one study, moderate or vigorous occupational activity, leisure activity, and commuting activity were each independently associated with reduced diabetes risk (7). Furthermore, in elderly women and men, bicycling and participation in sports have been found to be associated with reduced diabetes risk (8). However, the mechanism by which physical inactivity and obesity increase diabetes risk is incompletely understood. Physical activity appears to result in insulin-receptor up-regulation in muscle tissue and hence increased delivery of glucose and insulin to the muscles (9). Obesity increases peripheral insulin resistance and reduces beta-cell function (10, 11). There is also evidence that adipose tissue affects insulin metabolism through the release of free fatty acids and cytokines (10, 12).

In addition to these mechanisms, the role of the liver in the pathogenesis of type 2 diabetes is increasingly being recognized. Both directly determined liver fat content (13) and circulating levels of alanine aminotransferase (ALT) (14–16) and gamma-glutamyltransferase (GGT) (17–19), which reflect liver fat content, have been shown to be associated with diabetes risk, independently of alcohol consumption and other potential confounders, in prospective studies. Thus,

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obesity and physical activity may affect diabetes risk via an effect on liver fat content, which in turn influences insulin and glucose metabolism. A number of studies have shown that obesity in childhood and adulthood is associated with non-alcoholic fatty liver (20–22), and a recent prospective study with 150,233 person-years of follow-up found body mass index to be positively associated with increased risk of cirrhosis-related death or hospitalization among persons who consumed little or no alcohol (23). The majority of studies in this area to date have included males only, and to our knowledge no previous study has examined the independent associations of physical activity, body mass index, and waist:hip circumference ratio with ALT and GGT in a general population-based study. Previous studies have not examined whether associations with ALT and GGT explain any part of the relations of physical activity and obesity with type 2 diabetes.

Our primary aim in this study was to examine the independent associations of physical activity, body mass index, and waist:hip ratio with ALT and GGT among British women aged 60–79 years. Where associations were found, we then aimed to determine whether these associations explained any relation between the exposures and diabetes.

MATERIALS AND METHODS

Participants

Data from the British Women's Heart and Health Study were used. Full details on the selection of participants and measurements used in the study have been previously reported (24, 25). Between 1999 and 2001, 4,286 (60 percent of those eligible to participate) women aged 60–79 years who had been randomly selected from 23 British towns were interviewed and examined, completed medical questionnaires, and had detailed reviews of their medical records carried out. These women have been followed up over a median period of 4 years through flagging with the National Health Service central register for mortality data, 2-year (every other year) review of their medical records, and a mailed 3-year follow-up health questionnaire sent to all surviving participants between March and September of 2003. In the present paper, all analyses were cross-sectional and used data from the baseline assessment of the women. United Kingdom local and multicenter ethics committee approvals were obtained for the study.

Measurements

At the baseline examination, blood samples were taken after a minimum 6-hour fast. Serum was separated on-site within 30 minutes of venipuncture, stored at −4°C, and analyzed within 24 hours of venipuncture. Levels of ALT and GGT in serum were determined using an automated analyzer (Technicon Sequential Multiple Analyzer; Technicon Instruments Corporation, Tarrytown, New York). Glucose was measured in fasting venous samples by means of a glucose oxidase Trinder method (26) using a Flacor 600 automated analyzer (Bayer Healthcare Diagnostics, Bridgend, United Kingdom). Diabetes was defined, accord-ing to World Health Organization criteria (27), as a clinical diagnosis of diabetes (identified by medical record review or patient interview or by treatment with oral hypoglycemic agents or insulin) or a fasting blood glucose level equal to or above 7.0 mmol/liter. Standing height, weight, and waist and hip circumference measurements were all taken using standard procedures, as previously reported (24, 25). Body mass index was calculated as weight (kg) divided by the square of height (m^2).

We used the same physical activity questionnaire as was used in the British Regional Heart Study; this questionnaire has been shown to be associated with cardiovascular and diabetes outcomes (28, 29). Women were asked to report the average amount of time (in hours per week) they spent in eight groups of activity (walking, cycling, light gardening (e.g., pruning and watering), heavy gardening (e.g., digging and mowing), physical exercise (e.g., fitness/aerobics classes, jogging, tennis), do-it-yourself work on the house or car, light housework (e.g., cooking, washing up, dusting), and heavy housework (e.g., vacuuming, window cleaning)). In addition, they were asked to report whether their usual walking pace was slow, steady average, brisk, or fast (at least 4 miles/hour (6.4 km/hour)). The number of hours per week spent in moderate or vigorous activity (defined as brisk/fast walking, cycling, heavy gardening, physical exercise, or heavy housework) was calculated for each woman from her responses to these questions. Numbers of hours per week spent in moderate or vigorous activity were categorized as <2, 2–3, or >3. The majority of the women accumulated most of their activity through moderate-intensity activities, and when we repeated the analyses after excluding persons participating in vigorous activity, the results did not differ substantively from those presented here. Thus, our analysis was essentially an analysis of the effect of frequency of moderate-level activity among older women. Since the participants were all at or above the national retirement age for women in Britain (60 years), we did not inquire about occupational activity.

Information on adult occupational social class (based on the husband's longest-held job or the woman's longest-held job—whichever resulted in the highest social class category) and childhood occupational social class (Registrar General's classification: I, II, III–nonmanual, III–manual, IV, or V, with I being the highest (professionals) and V being the lowest (unskilled manual workers)), smoking (never, past, or current, including persons who reported quitting within the past 6 months), and alcohol consumption (daily/most days, weekends only, once/twice per month, special occasions only, or never) was obtained from questionnaire responses or the research nurse interviews.

Statistical analyses

Regression models were used to estimate age-adjusted means or prevalences of participant characteristics across the physical activity categories and across quarters of the body mass index and waist:hip ratio distributions. Multiple linear regression was used to assess the associations of physical activity, body mass index, and waist:hip ratio with

TABLE 1. Characteristics of participants by weekly duration of moderate/vigorous physical activity, British Women's Heart and Health Study, 1999–2001

| | Duration of moderate/vigorous physical activity | | | | | | |
| | <2 hours/week (n = 771) | | 2–3 hours/week (n = 543) | | >3 hours/week (n = 2,535) | | p trend |
	Age-adjusted mean or %	95% CI*	Age-adjusted mean or %	95% CI	Age-adjusted mean or %	95% CI	
Age (years)	70.3	69.9, 70.7	68.7	68.3, 69.1	68.4	68.2, 68.6	<0.001
Alanine aminotransferase (units/liter)	14.4	13.8, 15.0	14.3	13.6, 14.9	13.8	13.5, 14.1	0.05
Gamma-glutamyltransferase (units/liter)	34.4	32.0, 36.8	32.5	29.8, 35.2	27.4	26.1, 28.6	<0.001
Body mass index†	29.7	29.3, 30.0	28.3	27.9, 28.7	26.8	26.6, 27.0	<0.001
Waist:hip ratio (×100)	831.1	826.2, 836.2	820.1	814.4, 825.8	815.3	812.7, 817.9	<0.001
Ever smoking (%)	48.3	44.7, 52.0	45.1	41.0, 49.3	42.4	40.5, 44.4	0.003
Alcohol consumption (%)							
Daily alcohol drinking	13.3	10.9, 16.2	17.1	14.0, 20.7	20.2	18.6, 21.8	<0.001
No alcohol drinking (teetotaler)	22.9	19.8, 26.2	18.6	15.4, 22.1	15.6	14.2, 17.1	<0.001
Manual-labor social class (%)							
Adulthood	62.2	58.6, 65.7	55.8	51.6, 60.0	54.1	52.1, 56.0	<0.001
Childhood	84.1	81.3, 86.7	82.4	78.9, 85.3	77.7	76.0, 79.3	<0.001

* CI, confidence interval.
† Weight (kg)/height (m)^2.

results of liver function tests, taking account of potential covariates. In the first model, adjustment was made for age (continuous variable in years) only. Four other potential confounders (alcohol: five-level categorical variable; adult and childhood social class: each a six-level categorical variable; and smoking: three-level categorical variable) were added to the second model. In the third model, in addition to these confounders, physical activity (three-level categorical variable), body mass index (continuous variable), and waist:hip ratio (continuous variable) were entered simultaneously for determination of their independent effects. To determine whether any associations between exposures and diabetes were mediated by relations with results of liver function tests, we carried out stratified analyses (in persons with and without diabetes) and assessed the effect of adjusting for liver function in the exposure-diabetes associations using logistic regression.

RESULTS

Of the 4,286 women included in the analysis, 3,789 (88 percent) had adequate data on all measures of adiposity, physical activity, and liver function tests. Women without these complete data tended to be slightly older (mean age = 69.4 years (standard deviation, 5.7) vs. 68.8 years (standard deviation, 5.5); $p = 0.03$) and more likely to be in manual-labor social classes in childhood (83.5 percent vs. 79.6 percent; $p = 0.04$) and adulthood (68.2 percent vs. 55.9 percent; $p < 0.001$) than women with complete data.

Associations of physical activity, body mass index, and waist:hip ratio with ALT and GGT

Table 1 shows the characteristics of study participants by level of physical activity. Similar data presented by quarters of body mass index and waist:hip ratio are shown in tables 2 and 3. Levels of ALT and GGT both decreased linearly with increasing duration of moderate or vigorous physical activity. Greater duration of physical activity was also associated with reduced likelihood of ever smoking, being a teetotaler, and belonging to a manual-labor social class in either childhood or adulthood. Body mass index was positively and linearly associated with ALT and GGT. Body mass index was not associated with smoking, but women from a manual social class in either childhood or adulthood were more likely to have higher body mass indices. Waist:hip ratio was positively associated with both ALT and GGT and was greater among smokers and persons from manual social classes in adulthood but showed no association with childhood social class.

The age-adjusted linear trend of the association of physical activity with ALT was attenuated towards the null with additional adjustment for smoking, alcohol consumption, and adult and childhood social class; it was attenuated further when either body mass index or waist:hip ratio was added to the model (table 4). Both body mass index and waist:hip ratio contributed to this attenuation. GGT remained associated with physical activity in adjusted models (table 4). The positive age-adjusted linear associations of both body mass index and waist:hip ratio with ALT and GGT remained after adjustment for social and behavioral

TABLE 2.   Characteristics of participants by quarter of body mass index,* British Women's Heart and Health Study, 1999–2001

	Quarter of body mass index								p trend
	Lowest (15.3–24.2) (n = 954)		Second (24.3–26.9) (n = 952)		Third (27.0–30.3) (n = 951)		Highest (30.4–58.8) (n = 932)		
	Age-adjusted mean or %	95% CI†	Age-adjusted mean or %	95% CI	Age-adjusted mean or %	95% CI	Age-adjusted mean or %	95% CI	
Age (years)	69.2	68.9, 69.6	68.8	68.4, 69.1	68.8	68.5, 69.2	68.4	68.1, 68.7	0.002
Alanine aminotransferase (units/liter)	12.6	12.1, 13.1	13.6	13.1, 14.1	14.4	13.9, 14.9	15.4	14.9, 15.9	<0.001
Gamma-glutamyltransferase (units/liter)	25.8	23.7, 27.9	26.2	24.1, 28.2	30.2	28.2, 32.3	35.7	33.6, 37.8	<0.001
Waist:hip ratio (×100)	781.9	777.9, 785.9	809.7	805.7, 813.7	832.5	828.5, 836.4	852.6	848.6, 856.7	<0.001
Ever smoking (%)	44.2	41.1, 47.4	42.0	38.9, 45.2	45.5	42.3, 48.7	44.0	40.8, 47.2	0.7
Alcohol consumption (%)									
Daily alcohol drinking	23.0	20.3, 25.9	20.2	17.7, 23.0	17.7	15.4, 20.4	12.6	10.6, 15.0	<0.001
No alcohol drinking (teetotaler)	14.4	12.3, 16.9	16.8	14.5, 19.4	18.4	16.0, 21.1	19.7	17.2, 22.5	0.001
Manual-labor social class (%)									
Adulthood	50.9	47.8, 54.1	53.4	50.2, 56.5	56.0	52.9, 59.2	63.2	60.1, 66.2	<0.001
Childhood	76.5	73.7, 79.1	78.1	75.3, 80.6	77.7	75.0, 80.3	86.1	83.7, 88.1	<0.001

* Weight (kg)/height (m)^2.
† CI, confidence interval.

TABLE 3.   Characteristics of participants by quarter of waist:hip ratio, British Women's Heart and Health Study, 1999–2001

	Quarter of waist:hip ratio								p trend
	Lowest (579.1–769.6) (n = 948)		Second (769.7–814.4) (n = 949)		Third (814.5–863.4) (n = 952)		Highest (863.5–1,202.2) (n = 940)		
	Age-adjusted mean or %	95% CI*	Age-adjusted mean or %	95% CI	Age-adjusted mean or %	95% CI	Age-adjusted mean or %	95% CI	
Age (years)	68.2	67.8, 68.5	68.7	68.3, 69.0	69.0	68.7, 69.4	69.3	69.0, 69.7	<0.001
Alanine aminotransferase (units/liter)	12.7	12.2, 13.2	13.3	12.8, 13.8	14.2	13.7, 14.7	15.9	15.3, 16.4	<0.001
Gamma-glutamyltransferase (units/liter)	24.5	22.5, 26.6	27.5	25.5, 29.6	30.3	28.2, 32.4	35.4	33.3, 37.5	<0.001
Body mass index†	25.0	24.8, 25.3	26.9	26.6, 27.2	28.3	28.0, 28.6	30.1	27.8, 30.4	<0.001
Ever smoking (%)	37.5	34.4, 40.6	41.6	38.5, 44.8	46.4	43.3, 49.6	50.2	47.0, 53.4	<0.001
Alcohol consumption (%)									
Daily alcohol drinking	21.8	19.2, 24.6	17.4	15.0, 20.0	18.0	15.6, 20.7	16.6	14.3, 19.3	0.02
No alcohol drinking (teetotaler)	16.1	13.8, 18.7	17.0	14.7, 19.6	16.9	14.6, 19.5	19.4	16.9, 22.1	0.2
Manual-labor social class (%)									
Adulthood	49.8	46.6, 53.0	54.9	51.7, 58.0	59.6	56.4, 62.6	59.2	56.0, 62.3	<0.001
Childhood	78.1	75.3, 80.6	80.6	78.0, 83.0	79.7	77.1, 82.2	79.8	77.1, 82.2	0.4

* CI, confidence interval.
† Weight (kg)/height (m)^2.

TABLE 4.   Multivariable associations of moderate/vigorous physical activity with levels of alanine aminotransferase and gamma-glutamyltransferase, British Women's Heart and Health Study, 1999–2001

Weekly duration of moderate/ vigorous physical activity	Model 1*		Model 2†		Model 3‡	
	Mean difference	95% CI§	Mean difference	95% CI	Mean difference	95% CI
Alanine aminotransferase (units/liter)						
<2 hours	0		0		0	
2–3 hours	−0.18	−1.08, 0.72	−0.30	−1.26, 0.66	−0.04	−0.98, 0.91
>3 hours	−0.61	−1.29, 0.06	−0.67	−1.40, 0.06	−0.21	−0.94, 0.52
p trend	0.05		0.06		0.53	
Gamma-glutamyltransferase (units/liter)						
<2 hours	0		0		0	
2–3 hours	−1.91	−5.55, 1.73	−1.95	−5.62, 1.71	−1.01	−4.65, 2.64
>3 hours	−7.04	−9.77, −4.31	−6.90	−9.68, −4.10	−5.16	−7.97, −2.34
p trend	<0.001		<0.001		<0.001	

* Adjusted for age.
† Adjusted for age, smoking, alcohol consumption, adulthood social class, and childhood social class.
‡ Adjusted for age, smoking, alcohol consumption, adulthood social class, childhood social class, body mass index, and waist:hip ratio.
§ CI, confidence interval.

risk factors, including mutual adjustment for each other and adjustment for physical activity (table 5).

Figure 1 further demonstrates the independent effects of both physical activity and waist:hip ratio on GGT level, with the highest mean GGT value being seen in persons who were the least active and had the greatest waist:hip ratio and the lowest value being seen in persons who were the most active and had the lowest waist:hip ratio. Similar findings were found within strata of physical activity and within thirds of body mass index (data not shown).

Because alcohol consumption is strongly associated with raised levels of GGT, simple adjustment for alcohol in multivariable models may be insufficient to fully control for its confounding effects. Therefore, we repeated the analyses after stratifying the data by alcohol consumption. The results were similar among women who reported either never drinking or drinking only on special occasions (*n* = 2,046) and women who reported drinking at least once or twice a month (*n* = 1,862). For example, the fully adjusted change in ALT per standard-deviation increase in waist:hip ratio among the very rare drinkers was 13.9 (95 percent confidence interval (CI): 9.3, 18.5), and among women who reported drinking at least once or twice a month, it was 18.7 (95 percent CI: 14.0, 23.4) (*p* for difference between these estimates = 0.1). Similar results for the association of waist:hip ratio with GGT were 42.4 (95 percent CI: 25.5, 59.4) and 56.9 (95 percent CI: 37.8, 75.9), respectively (*p* for difference between these estimates = 0.3). We also repeated the analyses using waist circumference instead of waist:hip ratio and found that none of the results were substantially different from those presented here. Further-more, when we excluded women with cancer, diabetes, or heart failure (all of which may affect liver function), the

results, though less precise, were essentially the same as those presented in the tables.

The roles of ALT and GGT in explaining associations of body mass index and waist:hip ratio with diabetes

Among the 3,789 women included in this analysis, 374 (9.9 percent) had diabetes according to the definition of the World Health Organization. Both body mass index and waist:hip ratio were positively and linearly associated with diabetes prevalence (table 6). The associations of body mass index and waist:hip ratio with diabetes were somewhat attenuated after adjustment for physical activity, smoking, alcohol consumption, and childhood and adulthood social class, though strong associations remained. Adjustment for ALT and GGT resulted in further attenuation towards the null. For example, the lifestyle- and social-class-adjusted odds ratio comparing the top quarter of body mass index with the bottom quarter decreased from 2.90 to 2.38 with additional adjustment for ALT and GGT, and for similar comparisons using quarters of waist:hip ratio, there was an attenuation from 4.09 to 3.49. However, for both measures of obesity, strong linear and positive associations remained with diabetes in the fully adjusted models. The associations of body mass index and waist:hip ratio with ALT and GGT in both women with diabetes and women without diabetes were similar to those presented for the whole group in table 5, though the estimates among women with diabetes were less precise. Physical activity was strongly linearly and inversely associated with diabetes (*p* < 0.001). However, this association was attenuated towards the null after adjustment for body mass index and waist:hip ratio

TABLE 5. Multivariable associations of body mass index and waist:hip ratio with levels of alanine aminotransferase and gamma-glutamyltransferase, British Women's Heart and Health Study, 1999–2001

	Model 1*			Model 2†			Model 3‡		
	Mean difference	95% CI§	p value	Mean difference	95% CI	p value	Mean difference	95% CI	p value
Alanine aminotransferase (units/liter)									
Per 1-SD§ change (5.01) in body mass index¶	0.95	0.69, 1.20	<0.001	0.91	0.64, 1.18	<0.001	0.46	0.16, 0.75	0.003
Per 1-SD change (0.068) in waist:hip ratio	15.65	12.60, 18.70	<0.001	16.07	12.82, 19.31	<0.001	13.96	10.44, 17.48	<0.001
Gamma-glutamyltransferase (units/liter)									
Per 1-SD change (5.01) in body mass index	3.52	2.48, 4.57	<0.001	3.84	2.78, 4.90	<0.001	2.14	0.99, 3.30	<0.001
Per 1-SD change (0.068) in waist:hip ratio	54.06	41.66, 66.46	<0.001	50.76	38.13, 63.39	<0.001	39.44	25.89, 52.98	<0.001

* Adjusted for age.
† Adjusted for age, smoking, alcohol consumption, adulthood social class, and childhood social class.
‡ Adjusted for age, smoking, alcohol consumption, adulthood social class, childhood social class, physical activity, and body mass index or waist:hip ratio.
§ CI, confidence interval; SD, standard deviation.
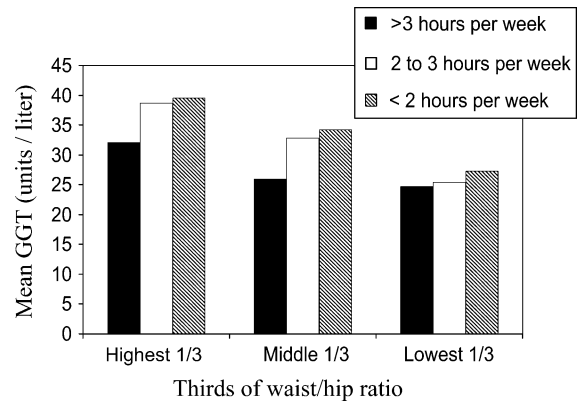¶ Weight (kg)/height (m)².

FIGURE 1. Mean level of gamma-glutamyltransferase (GGT) by weekly duration of moderate/vigorous physical activity and thirds of waist:hip ratio, British Women's Heart and Health Study, 1999–2001.

$(p = 0.12)$, with no further attenuation being seen upon adjustment for ALT and GGT.

DISCUSSION

Among British women aged 60–79 years, we found strong linear associations of both body mass index and waist:hip ratio with both ALT and GGT. These associations were independent of alcohol consumption, as demonstrated in stratified and multivariable analyses, and were also independent of physical activity, smoking, and childhood and adulthood socioeconomic position. The associations of body mass index and waist:hip ratio with these outcomes were also independent of each other. Furthermore, physical activity was independently (of measures of adiposity and other confounders) linearly associated with GGT, though it was not associated with ALT once measures of adiposity were taken into account. There was some attenuation of the strong associations of body mass index and waist:hip ratio with prevalent diabetes when adjustment for ALT and GGT was included in multivariable models.

The effect of general and central obesity on ALT and GGT levels may provide one mechanism for the link between obesity and diabetes risk. Prospective studies have shown that ALT and GGT are associated with increased risk of diabetes (14–19). These associations are believed to reflect the effect of fat accumulation in the liver (fatty liver) on diabetes risk (16). We have now demonstrated strong positive linear associations between body mass index and waist:hip ratio and ALT and GGT. Thus, this study provides an additional piece of evidence in the suggested causal pathway between obesity, through liver pathology, and diabetes risk. Similarly, the independent association of physical activity with GGT provides some evidence suggesting that one pathway linking physical activity to diabetes may be liver pathology. In this cross-sectional analysis, there was some attenuation of the associations of body mass index and waist:hip ratio with diabetes upon adjustment for ALT and GGT. However,

TABLE 6. Associations of body mass index* and waist:hip ratio with diabetes mellitus† and the effect on these associations of adjustment for levels of alanine aminotransferase and gamma-glutamyltransferase, British Women's Heart and Health Study, 1999–2001

	Model 1‡		Model 2§		Model 3¶	
	OR#	95% CI#	OR	95% CI	OR	95% CI
Quarter of body mass index						
Lowest	1		1		1	
Second	0.78	0.53, 1.13	0.77	0.52, 1.15	0.69	0.46, 1.04
Third	1.40	1.01, 1.95	1.41	0.99, 2.00	1.21	0.84, 1.74
Highest	3.07	2.28, 4.13	2.90	2.09, 4.04	2.38	1.69, 3.35
p trend	<0.001		<0.001		<0.001	
Quarter of waist:hip ratio						
Lowest	1		1		1	
Second	1.50	1.03, 2.20	1.45	0.98, 2.17	1.38	0.92, 2.09
Third	1.98	1.38, 3.86	1.84	1.25, 2.70	1.67	1.13, 2.48
Highest	4.47	3.20, 6.42	4.09	2.87, 5.83	3.49	2.42, 5.06
p trend	<0.001		<0.001		<0.001	

* Weight (kg)/height (m)^2.

† Defined according to the criteria of the World Health Organization (27).

‡ Adjusted for age.

§ Adjusted for age, physical activity, smoking, alcohol consumption, adulthood social class, and childhood social class.

¶ Adjusted for age, physical activity, smoking, alcohol consumption, adulthood social class, childhood social class, and levels of alanine aminotransferase and gamma-glutamyltransferase.

\# OR, odds ratio; CI, confidence interval.

further analyses using incident cases of diabetes are required to confirm these results. Although a number of studies have shown that body mass index and physical activity have independent effects on diabetes risk, a recent analysis of data from the Women's Health Study found that the magnitude of the association between body mass index and diabetes risk was greater than that of the association between physical activity and diabetes risk (3). The lack of an independent association between physical activity and ALT in our study may mean that the independent effect of physical activity on diabetes is expressed primarily through other mechanisms—for example, through an effect on peripheral (muscle) insulin receptors (9). Alternatively, greater measurement error in our assessment of physical activity as compared with our assessment of body mass index or waist:hip ratio (see below) may explain the somewhat weaker results for physical activity. Since most of the activity undertaken by these participants was of moderate intensity, it is possible that more vigorous activity has stronger associations with ALT and GGT. However, moderate-level physical activity has been found to be protective against type 2 diabetes (6, 7).

Study limitations

The majority (88 percent) of our participants had adequate data on all liver function tests, physical activity, body mass index, and waist:hip ratio. However, those without these data tended to be older and from more adverse social classes in childhood and adulthood. We adjusted for these factors in our multivariable analyses. This adjustment does not necessarily remove the potential for selection bias, but for our results to be importantly biased, one would have to assume that among women without complete data the association was either in the direction opposite that presented here or nonexistent. While we cannot rule out this possibility, it seems unlikely.

Our measure of physical activity relied on self-reporting rather than an objective measurement such as accelerometer readings. This measure has been used in a previous study of men and shown to predict disease outcomes with the strength and direction that would be anticipated (28, 29), but we have no information on the validity of its use in older women. However, self-reporting of physical activity level is common in large-scale epidemiologic studies; our questions have face validity; and we have found strong associations between our measure of physical activity and other characteristics, such as body mass index, waist:hip ratio (table 1), diabetes prevalence, insulin resistance, high density lipoprotein cholesterol level, and triglyceride level (data not shown), as one would expect. These associations were independent of the social and behavioral characteristics of the women. Despite these associations, it is likely that our assessment of physical activity had greater measurement error than our assessment of body mass index and waist:hip ratio; and this might, in part, explain the stronger and more robust associations observed between these anthropometric measures and both the liver function test results and diabetes as compared with similar associations between physical activity and these outcomes.

Our study was cross-sectional, and therefore we cannot exclude the possibility of reverse causality—that is, higher

levels of ALT and GGT resulting in greater body mass index and greater waist:hip ratio—though this seems unlikely. Furthermore, we currently have insufficient numbers of incident diabetes cases among these women to examine the effect of adjustment for ALT and GGT on associations between obesity measures and physical activity and diabetes. Although our cross-sectional analysis showed attenuation and provided some suggestion that the associations of body mass index and waist:hip ratio with diabetes may be partly mediated by liver pathology, further studies using incident data are required to confirm this. Finally, we analyzed older British women, over 99 percent of whom were described as White by the examining nurses; therefore, our results are not necessarily generalizable to men, younger persons, or persons from different ethnic groups.

Conclusion

In conclusion, we have shown that greater body mass index, greater waist:hip ratio, and lower levels of physical activity are independently associated with higher levels of GGT and that body mass index and waist:hip ratio are independently and positively associated with ALT. These findings provide some support for the suggestion that the relation between general and central obesity and diabetes risk is at least partly mediated by fat accumulation in the liver.

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