

# Total and Regional Adiposity and Cognitive Change in Older Adults

## *The Health, Aging and Body Composition (ABC) Study*

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**Objectives:** To investigate whether total and/or regional adiposity measured by anthropometry and radiographic studies influences cognitive decline in older adults and whether this association is explained by hormones and inflammatory factors known to be secreted by adipose tissue.

**Design:** Prospective cohort study.

**Setting:** Two clinical centers.

**Participants:** Three thousand fifty-four elderly individuals enrolled in the Health ABC Study. Adiposity measures included body mass index, waist circumference, sagittal diameter, total fat mass by dual-energy x-ray absorptiometry, and subcutaneous and visceral fat by abdominal computed tomography. We examined the association between baseline body fat measures and change in Modified Mini-Mental State Examination (3MS) score, sequentially adjusting for confounding and mediating variables, including comorbid diseases, adipocytokines, and sex hormones.

**Main Outcome Measure:** Scores from the 3MS, administered at the first, third, fifth, and eighth annual clinical examinations.

**Results:** All baseline adiposity measures varied significantly by sex. In mixed-effects models, the association between total and regional adiposity and change in 3MS score varied significantly by sex, with the highest adiposity tertile being associated with greater cognitive declines in men (for each adiposity measure,  $P < .05$ ) but not in women (for interaction,  $P < .05$ ). Total fat mass was significantly associated with greater change in 3MS scores among men (lowest tertile,  $-1.6$ ; middle tertile,  $-2.2$ ; highest tertile,  $-2.7$ ;  $P = .006$ ), even after adjusting for mediators.

**Conclusions:** Higher levels of all adiposity measures were associated with worsening cognitive function in men after controlling for metabolic disorders, adipocytokines, and sex hormone levels. Conversely, there was no association between adiposity and cognitive change in women.

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**Group Information:** The Health ABC Study investigators are listed at the end of this article.

**M**OST NATIONS ARE FACING growing rates of overweight and obesity, with latest global projections from the World Health Organization of approximately 1.6 billion overweight and 400 million obese adults.<sup>1</sup> Well-recognized adverse effects of overweight include type 2 diabetes, hypertension, and cardiovascular disease.

Obesity has also been found to be associated with risk of developing dementia after accounting for cardiovascular risk factors like hypertension and diabetes.<sup>2,3</sup> Overweight has been associated with cerebral atrophy<sup>4</sup> and cerebral white matter lesions.<sup>5</sup> Less is known about the effect of adiposity on rates of cognitive change in elderly people without dementia. More-

over, most studies use surrogate measures of adiposity like body mass index (BMI)<sup>6,7</sup> or waist circumference,<sup>8</sup> which may be less valid in older populations<sup>9</sup> than direct measurements of fat mass with whole-body dual-energy x-ray absorptiometry. Abdominal visceral fat measured by computed tomography is closely associated with metabolic disorders like diabetes, but no prior study has examined radiographically measured regional fat deposits and their effect on change in cognitive function. While prior studies have found that inflammatory factors are independently associated with cognitive decline,<sup>10</sup> none to date have examined the effect of adipose-derived hormones, or adipocytokines, on cognitive function and whether they explain the effect of adiposity on cognitive change. Therefore, it is un-

clear whether or not the body weight associations observed are due to total fat mass, specific fat deposits, or fat-derived hormones.

We analyzed data from participants enrolled in the Health, Aging and Body Composition (ABC) Study to examine associations between baseline measures of overall and regional adiposity and change in cognitive function. We examined whether or not adjusting for potentially mediating diseases, adipocytokines, and sex hormones would explain the association between adiposity and risk of cognitive change.

## METHODS

Participants enrolled in the Health ABC Study were well-functioning men and women aged between 70 and 79 years who were recruited from April 1997 to June 1998 from a clinical center in Pittsburgh, Pennsylvania, and Memphis, Tennessee. To be eligible, participants had to report no difficulty in walking 0.4 km (0.25 miles), climbing 10 steps, or performing activities of daily living. Individuals who required assistive ambulation devices or who had life-threatening cancers were excluded.

We used the baseline medical history, physical examination measurements, laboratory tests, radiographic assessments, and cognitive function data gathered in 1997-1998. Of the 3075 participants enrolled in the Health ABC Study, we excluded 21 because they did not have any measurements of total adiposity and another 7 individuals who were missing all Modified Mini-Mental State Examination (3MS) results at the 4 times, which resulted in 3054 individuals being included in our analytic cohort. The study was approved by the institutional review boards at the University of California-San Francisco, University of Pittsburgh, and University of Tennessee. All of the study participants provided written informed consent.

Weight was measured on a standard balance scale and height was measured with a stadiometer. Body mass index was calculated as weight in kilograms divided by height in meters squared. Total fat mass was measured by whole-body dual x-ray absorptiometry and analyzed by tertile. We evaluated 4 measures of regional adiposity, 2 anthropometric and 2 radiographic. Waist circumference was measured with a flexible tape measure at the participant's largest circumference. Abdominal sagittal diameter was measured with a Holtain-Kahn abdominal caliper while the participant lay supine. The lower blade of the caliper was placed under the small of the back and the upper blade was lowered to a mark midway between the iliac crests. Abdominal visceral and subcutaneous fat areas were measured by computed tomography. Visceral fat and subcutaneous abdominal fat was measured at the L4-L5 level. Fat areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area using Interactive Data Language software (ITT Visualization Solutions, Boulder, Colorado).

## COGNITIVE FUNCTION ASSESSMENT

The 3MS was administered to all participants during the baseline visit (year 1) and repeated at the third, fifth, and eighth annual examinations. This test is a brief general cognitive test with components for orientation, concentration, language, praxis, and immediate and delayed memory with a maximum score of 100.<sup>11</sup> The 3MS is more sensitive than the 30-point Mini-Mental State Examination, especially for mild cognitive change.<sup>11</sup> We examined cognitive decline by using the change in 3MS score from the baseline examination to the eighth follow-up examination.

## COVARIATES AND EXPLANATORY FACTORS

Racial group, age, sex, education, and smoking information was obtained. Physical activity was assessed using self-reported walking and exercise, with kilocalories per week to assigned activities. Literacy was assessed during the second annual visit using the Rapid Estimate of Adult Literacy in Medicine; scores lower than 60 indicated limited literacy.<sup>12</sup> Depressive symptoms were measured using the Center for Epidemiologic Study Depression Scale.<sup>13</sup> Each participant had seated systolic blood pressures measured with a manual sphygmomanometer. Participants were considered to have diabetes if they self-reported a diagnosis, used diabetes drugs, or if their fasting plasma glucose level was 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555) or their 2-hour postchallenge glucose level was 200 mg/dL or greater.

Participants underwent venipuncture after an overnight fast. Serum samples were frozen at -70°C. Fasting lipoproteins and fasting and 2-hour plasma glucose were measured. The allele producing the  $\epsilon 4$  type of apolipoprotein E was assessed and coded as present or not.<sup>14</sup> Serum creatinine was measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York), and estimated glomerular filtration rate was calculated.<sup>15</sup>

We evaluated 4 adipocytokines (adiponectin, IL-6 [interleukin 6], tumor necrosis factor  $\alpha$ , and plasminogen activator inhibitor-1). Adiponectin was measured in duplicate by radioimmunoassay. Interleukin 6 and tumor necrosis factor  $\alpha$  were measured in duplicate with enzyme-linked immunosorbent assay. Plasminogen activator inhibitor-1 was measured using a 2-site enzyme-linked immunosorbent assay.

At baseline, total testosterone was measured by a chemiluminescent immunoassay. At the third annual examination, bioavailable estradiol was measured by radioimmunoassay. All samples were measured in duplicate.

## STATISTICAL ANALYSIS

We used the  $\chi^2$  test and analysis of variance to examine whether baseline characteristics were associated with sex-specific total fat mass tertile. We evaluated the distribution of overall adiposity and regional adiposity separately by sex and race.

We determined the unadjusted association between sex-specific tertiles of each adiposity measure with change in 3MS score between baseline and the eighth annual clinical examination and tested for sex and race interaction. Because 3MS scores were negatively skewed, we used the Box-Cox method to find an appropriate transformation.<sup>16</sup> Because we found an interaction by sex with all adiposity measures, we stratified subsequent models by sex.

We used mixed-effects models with random participant-specific intercepts and slopes and an unstructured covariance matrix, allowing the use of all available data without imputation of any missing values. We adjusted for the fixed effects of time in years from the baseline cognitive measurement, potential baseline confounders, and their interactions with time. Baseline cognitive scores were included in every model. Cognitive scores were obtained from each model for every time and tertile and back-transformed to 3MS score. Changes in score were calculated by subtracting the score at baseline from the score at the final examination; standard errors were calculated by bootstrapping the resulting change in score with 1000 replications.<sup>17</sup> We adjusted for potential confounders in separate stages. First, we adjusted for demographic variables: age, race, education, physical activity, and literacy. We then added chronic risk factors: diabetes and systolic blood pressure. Next, we added adipocytokines to the model to determine whether or not they

**Table 1. Distribution of Adiposity Measures by Sex in the 3054 Health, Aging and Body Composition Study Participants**

Adiposity Measure	Mean (SD) by Sex and Adiposity Tertile <sup>a</sup>					
	Men			Women		
	Low	Middle	High	Low	Middle	High
Overall adiposity measure						
Total fat mass, kg	16.9 (3.0)	23.4 (1.6)	32.2 (5.1)	19.6 (3.6)	28.3 (2.2)	39.6 (6.6)
Body mass index <sup>b</sup>	22.9 (1.7)	27.2 (1.4)	32.8 (2.6)	22.1 (2.0)	27.4 (1.4)	34.5 (3.7)
Regional adiposity measure, cm						
Waist circumference	89.0 (8.0)	100.4 (2.5)	112.9 (6.9)	83.6 (6.6)	97.8 (3.1)	113.2 (9.0)
Sagittal diameter	19.3 (1.2)	22.4 (0.8)	26.2 (2.0)	18.2 (1.4)	21.7 (0.8)	25.8 (2.1)
Abdominal fat, cm <sup>2</sup>						
Visceral	84.6 (24.1)	144.1 (16.0)	235.2 (53.3)	71.0 (19.5)	122.8 (14.1)	199.9 (43.6)
Subcutaneous	140.0 (35.6)	219.3 (20.6)	326.1 (63.6)	210.5 (52.7)	327.1 (30.1)	477.6 (79.7)

<sup>a</sup>Sex-specific tertiles for fat mass, body mass index, waist circumference, sagittal diameter, abdominal visceral, and subcutaneous fat.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared. Body mass index groups are the following: less than 25, 25 to 30, and 30 or greater.

would explain the relationship between adiposity and cognitive change. In an exploratory analysis, we further adjusted for endogenous sex hormones. Lastly, we performed a sensitivity analysis, excluding participants with involuntary weight loss of 5% or more from baseline weight through the eighth clinical examination. Statistical analyses were performed using Stata, version 9 (Stata Corp, College Station, Texas).

## RESULTS

Of the 3054 participants, men had lower total fat mass (24.2 vs 29.2 kg,  $P < .001$ ), BMI (27.1 vs 27.7,  $P < .001$ ), and subcutaneous fat area (228 vs 339 cm<sup>2</sup>,  $P < .001$ ) values and greater abdominal visceral fat area (155 vs 131 cm<sup>2</sup>,  $P < .001$ ) than women (**Table 1**). The higher total fat mass tertile was associated with higher proportions of black race, lower educational attainment, and low literacy level, primarily in women (**Table 2**). Diabetes was significantly associated with a higher tertile of fat mass in both men and women. Most types of adipocytokine in men and women were significantly associated with fat mass; adiponectin was inversely associated with increased fat mass. Baseline 3MS score was not significantly associated with fat mass tertile in the overall population. However, the association with baseline 3MS score and fat mass varied significantly by sex ( $P < .001$ ), with a trend toward a positive association in men (mean 3MS [standard deviation (SD)] score: lowest fat mass tertile, 88.5 [9.4]; middle tertile, 89.6 [8.3]; highest tertile, 90.4 [7.7]) and women having an inverse association between fat mass and baseline 3MS score (lowest tertile, 91.2 [7.8]; middle tertile, 91.2 [7.5]; highest tertile, 89.9 [7.3]).

In **Table 3**, we show the predicted change in 3MS score between the baseline and eighth annual examination by each adiposity measure in tertiles for men and women. In unadjusted analyses, higher tertiles of total fat mass, sagittal diameter, and subcutaneous fat were associated with greater change in 3MS scores in men (total fat: lowest tertile, -1.6; middle tertile, -2.3; highest tertile, -2.7;  $P = .009$ ). Conversely, among women, higher tertiles of total fat mass and BMI were associated with less change in 3MS score, though higher waist circum-

ference was associated with greater change in score. In analyses adjusted for age, race, education, literacy, physical activity, systolic blood pressure, diabetes, IL-6, tumor necrosis factor  $\alpha$ , plasminogen activator inhibitor-1, and adiponectin, there were no significant associations between baseline adiposity measures and change in 3MS score in women. However higher tertiles of total fat mass, BMI, waist circumference, sagittal diameter, and subcutaneous fat were all associated with a significantly greater change in 3MS score in men, even after adjustment for covariates and potential mediators. There was a similar trend toward greater change in 3MS score with increasing tertile of abdominal visceral fat in men. Race did not modify the association between adiposity measures and change in 3MS score.

The **Figure** shows the adjusted change in 3MS score between the baseline and eighth annual examination for each of the 4 adiposity measures. Sex significantly modified the association between adiposity and change in 3MS score (for total fat mass, BMI, and abdominal subcutaneous fat,  $P < .001$ ; for visceral fat,  $P = .01$ ). To determine whether endogenous sex hormones may explain this sex interaction, we further adjusted for total testosterone and bioavailable estradiol. The interaction between sex and each adiposity measure remained robust (for total fat mass and BMI,  $P = .003$ ; for abdominal subcutaneous fat,  $P = .005$ ; for visceral fat,  $P = .05$ ). Finally, the exclusion of 676 individuals who unintentionally lost a significant amount of body weight did not affect our results.

## COMMENT

In this cohort of well-functioning older adults, higher tertiles of radiographically measured total fat mass and subcutaneous fat were associated with worsening cognitive function after 7 years in men. This association remained significant even after adjusting for potential explanatory links between adiposity and cognitive function, including metabolic risk factors and adipocytokines. We found a striking paradoxical sex interaction with increasing adiposity measures that showed trends

**Table 2. Characteristics of Men and Women by Total Fat Mass Tertile**

Characteristic	Men				Women			
	Mean (SD)			P Value <sup>a</sup>	Mean (SD)			P Value <sup>a</sup>
	Low (n = 493)	Middle (n = 493)	High (n = 493)		Low (n = 525)	Middle (n = 525)	High (n = 525)	
Age, y	73.9 (2.9)	73.9 (2.8)	73.6 (2.8)	.13	73.9 (3.0)	73.5 (2.8)	73.1 (2.8)	<.001
Black race, %	43	35	33	.002	34	43	61	<.001
<High school education, %	29	27	25	.36	18	20	31	<.001
<Ninth grade REALM level, %	28	30	27	.69	17	16	26	<.001
Self-rated fair/poor health, %	17	14	18	.17	11	16	21	<.001
Physical activity, kcal/wk <sup>b</sup>	1411 (2409)	1460 (2463)	1388 (2140)	.10	723 (1069)	689 (1266)	703 (1504)	.03
Current smoker, %	16	10	6	<.001	14	10	7	<.001
>1 Alcoholic drink/d, %	12	12	12	.99	5	3	2	.06
APOE ε4 carrier, %	28	29	26	.58	33	27	31	.10
Estimated GFR, mL/min/1.73 m <sup>2</sup>	75 (19)	73 (16)	74 (16)	.31	72 (16)	71 (15)	72 (17)	.051
Systolic blood pressure, mm Hg	135 (21)	135 (21)	135 (21)	.89	135 (21)	136 (21)	138 (21)	.03
Comorbid disorders, %								
Depression score ≥ 16	4	2	5	.16	5	7	5	.55
Hypertension	57	60	62	.25	58	67	74	<.001
Diabetes	21	27	33	<.001	14	22	28	<.001
Myocardial infarction	14	18	15	.21	8	9	7	.71
Stroke/TIA	9	8	7	.71	8	10	7	.14
Adipocytokine <sup>b</sup>								
Adiponectin, μg/mL	10.8 (6.3)	9.1 (5.1)	8.4 (4.9)	<.001	16.4 (8.0)	12.3 (6.4)	11.0 (6.2)	<.001
PAI-1, ng/mL	19.7 (17.3)	26.0 (20.2)	34.2 (23.5)	<.001	20.8 (20.3)	31.8 (24.3)	26.5 (27.5)	<.001
IL-6, pg/mL	2.5 (2.1)	2.2 (1.6)	2.6 (1.8)	.01	2.0 (1.8)	2.2 (1.7)	2.8 (2.2)	<.001
TNF-α, pg/mL	3.5 (1.7)	3.5 (1.4)	3.7 (1.6)	.08	3.2 (1.6)	3.4 (1.4)	3.5 (1.5)	<.001
Sex hormone								
Total testosterone, ng/dL <sup>b</sup>	0.85 (0.38)	0.84 (0.37)	0.82 (0.47)	.19	0.30 (0.18)	0.34 (0.31)	0.36 (0.22)	<.001
Estradiol, pg/mL <sup>b</sup>	32.1 (13.9)	30.6 (12.8)	30.8 (16.2)	.60	20.8 (31.2)	16.7 (27.0)	19.9 (23.7)	.01
Baseline 3MS score	88.5 (9.4)	89.6 (8.3)	90.4 (7.7)	.09	91.2 (7.8)	91.2 (7.5)	89.9 (7.3)	<.001

Abbreviations: GFR, glomerular filtration rate; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1; REALM, Rapid Estimate of Adult Literacy in Medicine; TIA, transient ischemic attack; TNF-α, tumor necrosis factor α; 3MS, Modified Mini-Mental State Examination.

SI conversion factors: To convert estradiol to picomoles per liter, multiply by 3.671; PAI-1 to picomoles per liter, multiply by 19.231; testosterone to nanomoles per liter, multiply by 0.0347.

<sup>a</sup>By  $\chi^2$  test for dichotomous variables and analysis of variance for continuous variables.

<sup>b</sup>Log-transformed for statistical comparison.

toward less cognitive change in women but greater cognitive change in men. This sex interaction was consistent with all adiposity variables and remained significant after adjustment for metabolic variables and sex hormone levels.

Several studies have examined the effect of overweight on cognitive function.<sup>2,6,7</sup> Some longitudinal studies have found that a higher BMI is associated with increased risk of developing dementia,<sup>18-21</sup> while others have found no association.<sup>22-24</sup> Fewer studies have evaluated the association between adiposity and cognitive function or decline in adults without dementia. We found 2 prospective studies that evaluated the effect of BMI on cognitive function.<sup>6,7</sup> The first observed 1423 individuals in the Framingham Heart Study for 4 to 6 years and found that higher BMI was associated with worse cognitive function scores in men,<sup>6,25</sup> with a significant interaction between obesity and sex ( $P < .02$ ). The second study was performed in 5607 postmenopausal Danish women observed for 7 years; it examined baseline body weight, yearly change in weight, and central fat mass by whole-body dual x-ray absorptiometry.<sup>7</sup> The authors found a protective association of body fat mass with cognitive impairment in the elderly women and showed that

those who lost the most weight had the worst cognitive performance at follow-up.<sup>7</sup> Neither of these studies had baseline measures of cognitive function or more precise measures of regional adiposity. Our findings that men with higher total fat mass have greater cognitive decline is consistent with the Framingham results, and our finding that women show a trend toward inverse associations with total fat mass and cognitive change is consistent with the Danish study. We have extended the literature by observing that total body fat and subcutaneous abdominal fat are the 2 adiposity measures that have the strongest effect on cognitive change in men.

There is less literature that evaluates the effects of regional adiposity on change in cognitive function. Two longitudinal studies have examined the effect of central adiposity on cognition, using either waist to hip ratio or sagittal abdominal diameter. The first, the Framingham Offspring Study, found that the individuals in the uppermost quartile of waist to hip ratio had significantly poorer performance on executive function and visuo-motor skills testing after a 12-year follow-up.<sup>8</sup> The second study observed 6583 members of Kaiser Permanente for 36 years and found that those in the highest quintile of sagittal abdominal diameter had a 3-fold in-



**Table 3. Change in 3MS Scores From Baseline to the Eighth Annual Examination**

Outcome Model	Men				Women			
	Mean (SE) Change in Score <sup>a</sup>			P Value <sup>b</sup>	Mean (SE) Change in Score <sup>a</sup>			P Value <sup>b</sup>
	Low	Middle	High		Low	Middle	High	
Total fat mass, kg								
Unadjusted	-1.61 (0.14)	-2.28 (0.13)	-2.66 (0.14)	.009	-3.11 (0.18)	-2.39 (0.15)	-2.35 (0.16)	.03
Multivariate-adjusted <sup>c</sup>	-1.55 (0.15)	-2.35 (0.16)	-2.72 (0.16)	.004	-2.88 (0.2)	-2.22 (0.16)	-2.05 (0.15)	.05
Fully adjusted	-1.65 (0.17)	-2.19 (0.16)	-2.69 (0.17)	.006	-2.87 (0.24)	-2.13 (0.19)	-2.2 (0.18)	.61
Body mass index <sup>d</sup>								
Unadjusted	-1.83 (0.14)	-2.25 (0.12)	-2.53 (0.15)	.14	-3.03 (0.19)	-2.37 (0.14)	-2.37 (0.16)	.01
Multivariate-adjusted <sup>c</sup>	-1.76 (0.17)	-2.31 (0.14)	-2.6 (0.18)	.08	-2.71 (0.2)	-2.29 (0.15)	-2.04 (0.17)	.01
Fully adjusted <sup>e</sup>	-1.77 (0.17)	-2.2 (0.16)	-2.64 (0.19)	.04	-2.76 (0.22)	-2.2 (0.18)	-2.12 (0.19)	.15
Waist circumference, cm								
Unadjusted	-1.75 (0.14)	-2.12 (0.13)	-2.68 (0.15)	.03	-2.52 (0.17)	-2.25 (0.12)	-3.04 (0.17)	.67
Multivariate-adjusted <sup>c</sup>	-1.73 (0.16)	-2.14 (0.14)	-2.75 (0.18)	.03	-2.32 (0.19)	-2.06 (0.13)	-2.73 (0.19)	.94
Fully adjusted <sup>e</sup>	-1.79 (0.18)	-2.05 (0.15)	-2.67 (0.18)	.03	-2.15 (0.22)	-2.02 (0.16)	-2.94 (0.22)	.27
Sagittal diameter, cm								
Unadjusted	-1.75 (0.13)	-2.2 (0.14)	-2.62 (0.15)	.09	-3.01 (0.19)	-2.49 (0.15)	-2.22 (0.14)	.01
Multivariate-adjusted <sup>c</sup>	-1.7 (0.16)	-2.23 (0.16)	-2.71 (0.16)	.06	-2.92 (0.21)	-2.28 (0.16)	-1.84 (0.15)	.002
Fully adjusted <sup>e</sup>	-1.73 (0.17)	-2.11 (0.16)	-2.68 (0.18)	.03	-2.81 (0.24)	-2.26 (0.19)	-1.96 (0.17)	.12
Visceral fat, cm <sup>2</sup>								
Unadjusted	-2 (0.16)	-2.07 (0.14)	-2.47 (0.13)	.08	-3.07 (0.18)	-2.27 (0.15)	-2.35 (0.15)	.21
Multivariate-adjusted <sup>c</sup>	-2.07 (0.18)	-2.07 (0.16)	-2.48 (0.14)	.06	-2.95 (0.2)	-2.12 (0.17)	-1.98 (0.14)	.05
Fully adjusted <sup>e</sup>	-2.11 (0.19)	-1.98 (0.17)	-2.37 (0.15)	.09	-2.91 (0.24)	-2.03 (0.2)	-2.12 (0.17)	.52
Subcutaneous fat, cm <sup>2</sup>								
Unadjusted	-1.21 (0.12)	-2.13 (0.14)	-3.23 (0.17)	<.001	-2.74 (0.19)	-2.27 (0.13)	-2.66 (0.15)	.25
Multivariate-adjusted <sup>c</sup>	-1.24 (0.14)	-2.1 (0.15)	-3.36 (0.19)	<.001	-2.55 (0.2)	-2.12 (0.14)	-2.33 (0.19)	.23
Fully adjusted <sup>e</sup>	-1.31 (0.16)	-2.03 (0.16)	-3.23 (0.21)	<.001	-2.48 (0.24)	-2.05 (0.17)	-2.51 (0.22)	.91

Abbreviation: 3MS, Modified Mini-Mental State Examination.

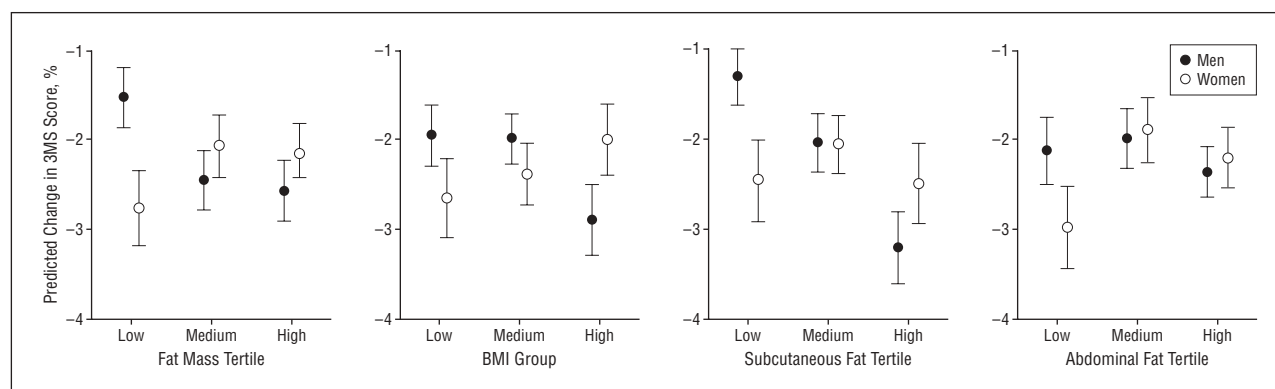
<sup>a</sup>Estimated by bootstrap sampling with 1000 replications.

<sup>b</sup>For trend across tertiles.

<sup>c</sup>Adjusted for age, race, education, literacy (in women), physical activity, diabetes, and systolic blood pressure.

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup>Multivariate model further adjusted for IL-6 (interleukin 6), tumor necrosis factor  $\alpha$ , plasminogen activator inhibitor-1, and adiponectin.



**Figure.** Tertiles of each adiposity measure by predicted change in Modified Mini-Mental State Examination (3MS) score adjusted for age, race, education, literacy (in women), physical activity, systolic blood pressure, diabetes, IL-6 (interleukin-6), tumor necrosis factor  $\alpha$ , plasminogen activator inhibitor-1, and adiponectin. Fat mass: for trend in men,  $P=.006$ ; in women,  $P=.62$ ; sex  $\times$  tertile interaction,  $P=.009$ . Body mass index (BMI) group: for trend in men,  $P=.04$ ; in women,  $P=.16$ ; sex  $\times$  tertile interaction,  $P<.001$ . Subcutaneous fat: for trend in men,  $P<.001$ ; in women,  $P=.9$ ; sex  $\times$  tertile interaction,  $P<.001$ . Abdominal fat: for trend in men,  $P=.1$ ; in women,  $P=.52$ ; sex  $\times$  tertile interaction,  $P=.01$ . Error bars indicate 95% confidence intervals.

creased risk of dementia independent of BMI and other cardiovascular risk factors.<sup>3</sup> Our study is the first to more closely examine regional adiposity measured radiographically. Surprisingly, our direct measure of visceral fat, which has been most closely tied to poor metabolic outcomes, had only a borderline significant association with cognitive change. The anthropometric measures of visceral

fat in our study (waist and sagittal diameter) only showed stronger associations with cognitive change in men. Because the previous studies have only found associations in the highest quartile or quintile of each anthropometric measurement, it is possible that their findings correspond to higher levels of overall obesity rather than to visceral adiposity.

We evaluated the effect of many potential mediators that may lie in the causal pathway between adiposity and change in cognition. We adjusted for diabetes and blood pressure and novel fat-secreted hormones and inflammatory factors.<sup>26</sup> The observed sex difference appeared strong and consistent for all fat measures and was only slightly attenuated with additional adjustment for adipocytokines and metabolic variables, such as high-density lipoprotein, insulin, and triglycerides. Endogenous sex hormones did not mediate this sex interaction. Other unmeasured metabolic and disease differences, such as the severity of hepatic or peripheral insulin resistance, intramyocellular steatosis, or newer adipocyte hormones, may provide additional mechanistic links to explain this sex interaction.

There are several possible biologic mechanisms that link adipose tissue to cognitive impairment. Some have proposed that adiposity in fetal development may influence cerebrovascular function and dementia risk.<sup>27,28</sup> Second, adipose tissue hormones that cross the blood-brain barrier may influence brain function and health by affecting energy balance mechanisms and memory.<sup>29,30</sup> Another possible mechanism is intrinsic differences in brain structure and function that can influence adiposity through energy homeostasis, reward, and other behavioral pathways.<sup>28</sup>

While our study stands apart from others, with radiographically measured adiposity, adipocytokines, and repeated measures of cognitive function, we cannot determine if there would be different effects with tests of other cognitive domains. We cannot determine whether the cognitive change that occurred was due to underlying Alzheimer disease or vascular dementia processes. Although we did not exclude participants with clinical dementia from the Health ABC Study, our cohort may represent healthy survivors, as they had no evidence of significant physical disability during the baseline examination, and it is possible that effect of adiposity on cognition differs in other, more frail individuals.

In conclusion, increasing levels of total fat mass, BMI, waist circumference, sagittal diameter, and subcutaneous abdominal fat are strongly associated with worsening cognitive function in men after controlling for metabolic disorders and adipocytokines. A more direct measure of visceral fat was not significantly associated with cognitive change. Women show trends toward inverse associations, with higher levels of adiposity being associated with less cognitive change. Traditional metabolic factors, adipocytokines, and sex hormones do not explain this sex difference. Future studies should confirm these longitudinal associations with adiposity and cognitive change and investigate why adiposity has inverse associations in men and women.

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