A 24-year follow-up of body mass index and cerebral atrophy

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Abstract—*Objective:* To investigate the longitudinal relationship between body mass index (BMI), a major vascular risk factor, and cerebral atrophy, a marker of neurodegeneration, in a population-based sample of middle-aged women. *Methods:* A representative sample of 290 women born in 1908, 1914, 1918, and 1922 was examined in 1968 to 1969, 1974 to 1975, 1980 to 1981, and 1992 to 1993 as part of the Population Study of Women in Göteborg, Sweden. At each examination, women completed a survey on a variety of health and lifestyle factors and underwent anthropometric, clinical, and neuropsychiatric assessments and blood collection. Atrophy of the temporal, frontal, occipital, and parietal lobes was measured on CT in 1992 when participants were age 70 to 84. Univariate and multivariate regression analyses were used to assess the relationship between BMI and brain measures. *Results:* Women with atrophy of the temporal lobe were, on average, 1.1 to 1.5 kg/m^2 higher in BMI at all examinations than women without temporal atrophy ($p < 0.05$). Multivariate analyses showed that age and BMI were the only significant predictors of temporal atrophy. Risk of temporal atrophy increased 13 to 16% per 1.0-kg/m^2 increase in BMI ($p < 0.05$). There were no associations between BMI and atrophy measured at three other brain locations. *Conclusion:* Overweight and obesity throughout adult life may contribute to the development of temporal atrophy in women.

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Overweight has recently come to the forefront as a risk factor for Alzheimer disease (AD).[1] As alterations in the brain underlie the symptoms characteristic of a clinical diagnosis of AD, it is important to assess the relationship between risk factors that have been associated with disease and corresponding brain pathologies. This will aid in the elucidation of biologic mechanisms whereby a risk factor may influence disease.

Overweight presents a serious public health problem in aging Western societies, where overweight and obesity are increasing at epidemic proportions.[2-5] The prevalence of overweight and obesity is >60% among adults in the United States and >50% in Europe,[2,4,5] with the highest prevalence observed among adults age 50 and older.[2,4] As overweight and obesity increase risk for vascular disorders,[6] overweight and obesity may be risk factors for cerebral degeneration.

Cerebral atrophy, a manifestation of neuronal degeneration, contributes to cognitive decline and dementia.[7-9] Atrophy of the temporal lobe, an area that is highly susceptible to the effects of ischemia and other vascular insults to the brain,[10] appears to be an early hallmark of AD.[7] In epidemiologic studies, cerebral atrophy has been related to a variety of vascular factors such as hypertension,[11-13] declining blood pressure over time,[14] cerebrovascular and cardiovascular disease,[12] diabetes,[15] smoking,[11] and high alcohol intake.[16,17] As a major vascular risk factor, overweight may trigger cerebral atrophy directly[18-20] or secondarily by leading to or exacerbating the aforementioned vascular factors such as high blood pressure.

We recently reported that overweight preceded AD in women followed from age 70 to 88[1] and was related to the occurrence of white matter lesions in a subset of those women.[21] Therefore, it seemed biologically plausible that the role of overweight and obesity may be multifactorial and related to cerebral atrophy, as well. We examined body mass index (BMI) and waist-to-hip ratio (WHR) in relationship to cerebral atrophy in a representative sample of women followed from 1968 to 1992 as part of the Population Study of Women (PSW) in Göteborg, Sweden.

Materials and methods. *Participant selection.* This analysis originates from the PSW, a prospective population survey of women in Göteborg, Sweden. PSW began in 1968 to 1969 with a baseline examination of a representative sample of 1,462 women

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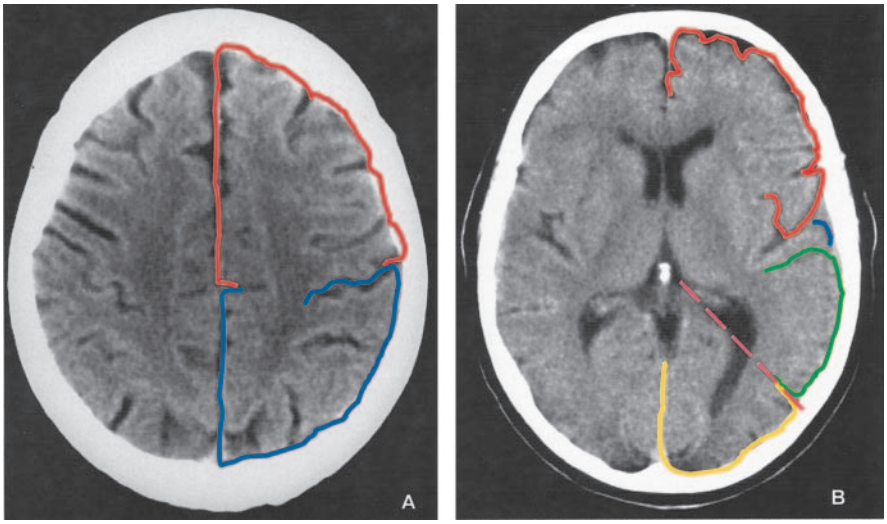

Figure. Examples of regions evaluated during the assessment of cortical atrophy. The borders of the frontal cortex are represented in red, the temporal cortex in green, the parietal cortex in blue, and the occipital cortex in yellow. (A) Section at the level of the centra semiovalia. (B) Section at the level of the trigones of lateral ventricles. The dashed line following the internal border of the ventricles is drawn to distinguish the temporal from the occipital region. During the visual evaluation, all pertinent slices were used to assess the atrophy in the four different regions. (CT scans from the Population Study of Women in Göteborg, Sweden, in 1992. Drawings made by Michela Simoni, MD, Department of Neurology, University of Florence, Italy.)

(90.1% participation rate) born in 1908, 1914, 1918, 1922, and 1930 (ages 60, 54, 50, 46, and 38 years at that time).[22] Among these, 1,090 were born in 1908 to 1922. The sample was obtained from the Revenue Office Register. Participants were re-examined in 1974,[23] 1980,[24] and 1992.[25] Informed consent was obtained from all participants and/or their relatives. The study was approved by the Ethics Committee for Medical Research of Göteborg University.

In 1992 to 1993, 837 surviving women born in 1908, 1914, 1918, and 1922 and living in Göteborg were invited to take part in the study. Of those, 559 (66.8%) agreed to take part in a psychiatric examination (19 born in 1908, 70 born in 1914, 215 born in 1918, and 255 born in 1922). Women born in 1930 were not invited to participate in the psychiatric examination.

All women participating in the psychiatric examination in 1992 to 1993 were invited to undergo CT of the brain, and 290 accepted (6 born in 1908, 35 born in 1914, 110 born in 1918, and 139 born in 1922).

Methods. At each examination year, participants underwent a physical examination performed by a physician, an EKG, a chest radiograph, and a battery of blood tests. Women were also surveyed about a variety of background factors such as educational level, socioeconomic status (SES), smoking habits, alcohol intake, physical activity, medication use, and medical history. Clinical measurements of weight, height, waist and hip circumferences, and systolic (SBP) and diastolic (DBP) blood pressures were performed.[26] Body height was measured without shoes to the nearest 0.5 cm in 1968 and to the nearest 0.1 cm in 1974, 1980, and 1992. Body weight was measured to the nearest 0.1 kg using a balance scale.

In 1992, a psychiatric examination was performed by a psychiatrist.[23,27] The psychiatric examination was semistructured and included tests of mental functioning, including the Mini-Mental State Examination (MMSE),[28] ratings of psychiatric symptoms and signs during the preceding month in accordance with the Comprehensive Psychopathological Rating Scale,[29] and ratings of dementia symptoms.[30] In a semistructured telephone interview, close informants were asked about cognitive and psychiatric symptoms in the participants. Dementia and other mental disorders were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (3rd rev. ed.),[31] as previously described.[30]

CT of the brain. All CT scans were performed without contrast enhancement and with 10-mm continuous slices. The CT scans were examined by an experienced radiologist, who was blind to the results of the neuropsychiatric examination. Brain atrophy was evaluated by rating cortical atrophy and determination of linear measurements of the ventricular width. The occipital, parietal, frontal, and temporal lobes were categorized using a 3-point scale (normal vs mild vs moderate or severe) according to the estimated extent of cortical atrophy. The figure illustrates the brain areas measured for determination of atrophy of the occipital, parietal, frontal, and temporal lobes in this study. The following linear distances were determined using a transparent metric ruler as described by deLeon et al.[32]: 1) the bifrontal span of the lateral ventricle, 2) the width of the lateral ventricles at the head of the caudate nucleus, 3) the sum of the separate widths of the left and right sylvian fissures, 4) the minimum width of the bodies of the lateral ventricles at the waist, and 5) the width of the third ventricle.

The interobserver measure of agreement for the presence vs absence of atrophy was studied in 140 CT scans that were blindly re-evaluated in 2002 by a neurologist trained in CT evaluations (Dr. Michela Simoni, Department of Neurology, University of Florence, Italy). The interobserver agreement was 73% for temporal atrophy (Spearman correlation = 0.43, $p < 0.001$; and $\kappa = 0.43$, $p < 0.001$), 69% for frontal atrophy (Spearman correlation = 0.35, $p < 0.001$; and $\kappa = 0.34$, $p < 0.001$), 70% for occipital atrophy (Spearman correlation = 0.29, $p < 0.001$; and $\kappa = 0.43$, $p = 0.001$), and 70% for parietal atrophy (Spearman correlation = 0.36, $p < 0.001$; and $\kappa = 0.35$, $p < 0.001$).

Statistical analyses. Atrophy was scored as none, mild, or moderate to severe. For statistical analyses, atrophy was considered as absent vs present and by increasing severity. BMI was calculated as kilograms per square meter, and WHR was calculated as the ratio of waist circumference to hip circumference. Participants were classified as overweight or obese on the basis of a BMI of $\geq$25 kg/m^2 and WHR of $\geq$0.80.[33,34] BMI cutpoints of $<$18.49, 18.5 to 22.49, 22.50 to 24.99, 25.00 to 27.49, 27.50 to 29.99, and $\geq$30 kg/m^2 were used to assess whether there was a J-shaped relationship between BMI and atrophy. Individual change in BMI over the course of the observational period was considered in two ways: 1) as trends in BMI from examination to examination (i.e., fluctuation vs consistent gain vs maintenance or decline in BMI) and 2) as the effects of 5, 10, 15, or 20% increases in BMI from 1968 to 1992.

Diagnoses of myocardial infarction, stroke, and diabetes were based on self-reports and clinical examinations (including EKG and blood samples), case records, and the hospital discharge register. A summary variable was created that represented the reporting of any of these medical events during the 24-year follow-up period. Level of education (completing $\leq$6 years vs $>$6 years of compulsory education) and SES were based on responses to the 1968 to 1969 survey. Alcohol consumption was defined as ever vs never in 1968. Cigarette smoking was defined based on participant responses in 1992 as ever vs never smoked.

Means and standard deviations were calculated for all quantitative variables. Relationships between atrophy and BMI, WHR, SBP, DBP, cardiovascular disease, stroke, diabetes, drug treatment for hypertension, hormone replacement therapy, smoking, alcohol intake, blood cholesterol and triglyceride levels, SES, and education were assessed using ANOVA and tests for linear trend for continuous variables. χ^2 analysis with the Fisher exact test was used for dichotomous variables. Univariate logistic regression analyses were also used for continuous and categorical variables. Multivariate logistic regression models were performed to assess

Table 1 *Characteristics of women who had CT in 1992 at each examination*

Characteristic	1968 mean ± SD (n)	1974 mean ± SD (n)	1980 mean ± SD (n)	1992 mean ± SD (n)
BMI, kg/m^2	24.2 ± 3.6	24.6 ± 3.7	25.0 ± 3.8	26.3 ± 4.4
	(290)	(286)	(275)	(288)
WHR	0.73 ± 0.05	0.78 ± 0.05	0.80 ± 0.07	0.83 ± 0.06
	(283)	(286)	(272)	(286)
Systolic blood pressure, mm Hg	132.4 ± 19.3	134.9 ± 19.9	146.9 ± 22.9	160.2 ± 23.9
	(290)	(286)	(275)	(290)
Diastolic blood pressure, mm Hg	82.6 ± 9.6	84.2 ± 9.4	85.6 ± 10.6	82.0 ± 10.2
	(290)	(286)	(275)	(290)
Over the 24-y follow-up period	n	%		
Stroke	290	5.2		
Myocardial infarction	290	4.1		
Diabetes	290	7.9		
Temporal atrophy	290	49.7		
Frontal atrophy	290	37.2		
Occipital atrophy	290	36.9		
Parietal atrophy	290	38.6		
High (>6 y) education	289	31.5		

BMI = body mass index; WHR = waist-to-hip ratio.

the strength of the relationship between atrophy and BMI and WHR against a background of potential confounding factors. Covariates were included in multivariate models if they met the criteria of $p < 0.05$ in univariate analyses. In all analyses, concurrent (same examination year) measures of BMI, WHR, SBP, DBP, cholesterol, and triglycerides were included in individual models. Linear tests for trend and ordinal regression analyses were used to assess the relationship between BMI and severity of atrophy. Two-tailed tests were used in all analyses at a significance level of $p < 0.05$.

Results. Characteristics of women who participated in the CT scan and had BMI measurements are shown in table 1. As expected, the average BMI and WHR increased with age, as did the percentage of women who presented with brain atrophy at any location (table 2). Overall, the sample experienced a mean gain in BMI of 2.1 ± 3.1 kg/m^2 over the 24-year follow-up period. Whereas the absolute change in BMI varied by cohort, the overall trend was a linear increase with age ($p < 0.001$). Participants and nonparticipants in the CT examination did not differ regarding a large number of factors studied, including BMI, WHR, SBP, DBP, blood cholesterol and triglyceride levels, education, and occurrence of stroke, diabetes, and myocardial infarction.

A high BMI, but not WHR, at each examination year was associated with atrophy of the temporal lobe (table 3). There were no associations between anthropometric measures and cerebral atrophy at other locations. Even when adjusted for a variety of potential confounding factors in multivariate regression models, the relationship between BMI and temporal atrophy remained strong (table 4). Severity of atrophy was not related to increasing levels of BMI.

Although it was a high average BMI that was associated with temporal atrophy, one may hypothesize that those with the lowest BMI at baseline are also at risk for atrophy due to compromised nutritional status or underlying disease irrespective of age. Of the eight women who had a BMI of <18.5 kg/m^2 in 1968, 50% exhibited temporal atrophy in 1992 and 50% did not. No suggestion of a J-shaped relationship between BMI and temporal atrophy was observed.

Complete data on changes in BMI over the entire follow-up period were available on 275 women. Of those, 74.2% (n = 204) experienced both increases and decreases in BMI during the follow-up period, 3.3% (n = 9) consistently maintained or lost weight, and 22.5% (n = 62) experienced an increase in BMI at every examination. These types of changes in BMI were not related to temporal atrophy ($p = 0.599$, age adjusted). Increases in BMI as 5, 10, 15, and 20% of baseline over the 24-year follow-up were also not related to temporal atrophy.

We chose not to exclude 11 women who were demented from our analyses. Although there was a higher percentage of demented with temporal atrophy vs without (6.3 vs 1.4%; $p = 0.034$), there were no differences in the proportion of demented for other atrophy locations.

Discussion. We found a relationship between higher BMI over a 24-year follow-up period and brain atrophy of the temporal lobe in elderly women. The average BMI of women who exhibited temporal atrophy in 1992 was not an overweight BMI (≥25 kg/m^2) at every examination but was consistently higher than that of women who did not develop atrophy. The relationship between BMI and temporal atrophy did not diminish after adjustment for a

Table 2 *Anthropometric and atrophy measurements in women born in 1908, 1914, 1918, and 1922 who had CT in 1992*

	Birth year 1908 Mean ± SD (range)	Birth year 1914 Mean ± SD (range)	Birth year 1918 Mean ± SD (range)	Birth year 1922 Mean ± SD (range)	*p* for linearity*
Baseline examination, 1968					
BMI, kg/m^2	26.2 ± 1.0	24.9 ± 0.7	24.6 ± 0.4	23.7 ± 0.2	0.007
	(24.3–29.3)	(17.8–34.2)	(17.4–38.4)	(17.5–37.3)	
	n = 6	n = 35	n = 110	n = 139	
WHR	0.77 ± 0.03	0.74 ± 0.01	0.73 ± 0.004	0.73 ± 0.004	0.024
	(0.68–0.88)	(0.65–0.90)	(0.61–0.84)	(0.63–0.88)	
	n = 6	n = 35	n = 107	n = 135	
Follow-up examination, 1974					
BMI, kg/m^2	27.2 ± 1.3	25.8 ± 0.7	24.9 ± 0.4	24.0 ± 0.3	0.001
	(24.4–32.6)	(0.7–17.2)	16.3–37.8	15.9–32.5	
	n = 6	n = 35	n = 109	n = 136	
WHR	0.80 ± 0.03	0.80 ± 0.01	0.78 ± 0.01	0.77 ± 0.004	0.012
	(0.72–0.93)	(0.68–0.98)	(0.64–0.93)	(0.66–0.93)	
	n = 6	n = 35	n = 109	n = 136	
Follow-up examination, 1980					
BMI, kg/m^2	27.0 ± 0.9	25.7 ± 0.7	25.2 ± 0.4	24.6 ± 0.3	0.035
	(23.8–30.1)	(18.2–34.2)	(17.1–39.5)	(18.5–34.6)	
	n = 6	n = 35	n = 106	n = 128	
WHR	0.85 ± 0.02	0.81 ± 0.01	0.80 ± 0.01	0.80 ± 0.01	0.407
	(0.78–0.89)	(0.67–0.94)	(0.66–0.99)	(0.69–1.06)	
	n = 6	n = 35	n = 106	n = 126	
Follow-up examination, 1992					
BMI, kg/m^2	25.4 ± 1.2	26.1 ± 0.8	26.3 ± 0.5	26.6 ± 0.3	0.522
	(20.8–29.7)	(17.9–33.4)	(16.3–46.2)	(18.5–48.6)	
	n = 6	n = 35	n = 110	n = 156	
WHR	0.85 ± 0.02	0.83 ± 0.01	0.83 ± 0.01	0.82 ± 0.01	0.534
	(0.78–0.91)	(0.70–0.96)	(0.64–0.96)	(0.70–1.01)	
	n = 6	n = 35	n = 109	n = 155	
Atrophy	Birth year 1908 n/total (%)	Birth year 1914 n/total (%)	Birth year 1918 n/total (%)	Birth year 1922 n/total (%)	
Temporal	6/6 (100)	24/35 (68.6)	56/110 (50.9)	58/139 (41.7)	0.001
Frontal	3/6 (50.0)	19/35 (54.3)	42/110 (38.2)	44/139 (31.7)	0.020
Occipital	6/6 (100.0)	18/35 (51.4)	49/110 (44.5)	34/139 (24.5)	0.000
Parietal	6/6 (100.0)	16/35 (45.7)	45/110 (40.9)	45/139 (32.4)	0.012

* *p* values for continuous variables correspond to the significance of a linear trend with age.

BMI = body mass index; WHR = waist-to-hip ratio.

number of potential confounding factors. In addition, changes in BMI over time were not related to temporal atrophy, nor was central adiposity related to atrophy.

That a high BMI increases risk for temporal atrophy both longitudinally and cross-sectionally is not surprising. First, recent data suggest that high BMI is a risk factor for AD[1] and precedes the onset of clinical dementia. Temporal atrophy may also precede the clinical symptoms of AD[7] and, on CT, is a likely marker of cerebral degeneration and neuronal death, events that lead to symptoms of dementia. As atrophy may precede and/or accelerate dementia processes, cerebral degeneration may be one pathologic mechanism whereby a high BMI increases dementia risk. Second, cerebral atrophy may result from neu-

Table 3 *BMI related to cerebral atrophy measures in 290 women, after adjustment for age*

Cerebral atrophy	No atrophy	Atrophy	*p* Value
Temporal lobe atrophy	n = 146	n = 144	
Age, y	72.1 (70–78)	73.5 (70–84)	0.000
BMI in 1968, kg/m^2	23.7 ± 3.4	24.8 ± 3.7	0.058
BMI in 1974, kg/m^2	24.0 ± 3.6	25.3 ± 3.7	0.019
BMI in 1980, kg/m^2	24.3 ± 3.6	25.8 ± 3.7	0.004
BMI in 1992, kg/m^2	25.8 ± 3.8	27.0 ± 4.7	0.007
Frontal lobe atrophy	n = 182	n = 108	
Age, y	72.4 (70–84)	73.4 (70–84)	0.017
BMI in 1968, kg/m^2	23.9 ± 3.5	24.7 ± 3.7	0.222
BMI in 1974, kg/m^2	24.5 ± 3.7	24.8 ± 3.7	0.797
BMI in 1980, kg/m^2	24.9 ± 3.8	25.2 ± 3.6	0.808
BMI in 1992, kg/m^2	26.3 ± 4.3	26.5 ± 4.5	0.540
Occipital lobe atrophy	n = 183	n = 107	
Age, y	72.1 (70–78)	74.0 (70–84)	0.000
BMI in 1968, kg/m^2	24.3 ± 3.6	24.1 ± 3.6	0.229
BMI in 1974, kg/m^2	24.7 ± 3.8	24.5 ± 3.4	0.159
BMI in 1980, kg/m^2	25.2 ± 3.9	24.7 ± 3.5	0.077
BMI in 1992, kg/m^2	26.6 ± 4.4	25.9 ± 4.2	0.202
Parietal lobe atrophy	n = 178	n = 112	
Age	72.3 (70–78)	73.5 (70–84)	0.002
BMI in 1968, kg/m^2	24.4 ± 3.8	24.1 ± 3.3	0.224
BMI in 1974, kg/m^2	24.8 ± 4.0	24.3 ± 3.0	0.100
BMI in 1980, kg/m^2	25.3 ± 4.1	24.6 ± 3.1	0.068
BMI in 1992, kg/m^2	26.7 ± 4.4	25.9 ± 4.2	0.239

Values are means (range) or means ± SD.

BMI = body mass index.

Table 4 *Multivariate risk models relating BMI to temporal atrophy in women*

Variable	Odds ratio (95% CI)*	*p* Value
BMI in 1968	1.12 (1.02–1.23)	0.022
BMI in 1974	1.14 (1.04–1.24)	0.006
BMI in 1980	1.13 (1.03–1.24)	0.009
BMI in 1992	1.11 (1.03–1.19)	0.006

* Risk ratios and 95% CIs were calculated using logistic regression analyses and adjusted for age, diastolic blood pressure, serum triglycerides, education, smoking, socioeconomic status, and the presence of any psychiatric disorder in each model. The odds ratios presented for body mass index (BMI) are per 1.0-kg/m^2 increase.

ronal apoptosis with a consequent decrease in cortical synaptic density. Age-related neuronal loss appears to be accelerated by a number of vascular factors that increase ischemia.[35,36] Obesity has been related to ischemia, in addition to a variety of vascular pathologies that are also potentially related to atrophy, including carotid artery wall thickening,[19] vascular and coronary endothelial dysfunction,[18,20,37,38] peripheral resistance, arterial stiffness,[39] ventricular hypertrophy, and increased sympathetic activity, intravascular volume, cardiac output, lipid levels,[40] and platelet aggregation.[39,41] Third, obesity may increase cortisol secretion,[42] which may lead to atrophy.[43] Thus, there are numerous biologically plausible mechanisms, direct and indirect, whereby overweight or obesity may lead to or enhance the progression of brain atrophy.

Among the strengths of this study are the lengthy follow-up, the high age and representativeness of the sample, the comprehensive examinations, and a clinical anthropometric assessment. However, there are also some limitations and methodologic factors that need to be addressed. First, although our data cannot be used to make causal inferences about the relationship between BMI and atrophy, we can address temporality to some extent as it is unlikely that cerebral atrophy was present in 1968 to 1969 in most of these women. However, irrespective of temporality, the relationship between BMI and atrophy was strong even when adjusted for multiple factors. Second, atrophy was measured using CT, which is less sensitive for detecting medial temporal lobe structures than MRI and may be affected by bone-hardening artifacts.[44] Furthermore, temporal atrophy was measured with a visual rating that is less reliable than volumetric measures. In this study, interobserver agreement for temporal atrophy was moderate ($\kappa = 0.43$), whereas agreement for the other cortical ratings was fair ($\kappa = 0.29$ to 0.36).[45] Although the agreement between independent measures may be slightly low, this will most likely attenuate the observed relationship. It may also explain why we only found an association between BMI and the presence (vs severity) of temporal atrophy and no association between BMI and atrophy at other locations. However, visual rating of the temporal lobe has been found to be highly predictive for the discrimination of AD vs control patients (sensitivity 95% and specificity 98%),[46] and temporal lobe atrophy is highly predictive for other forms of dementia, such as vascular dementia, frontal lobe dementia, and unspecified dementias. It appears that CT is comparable to MRI for detecting brain atrophy.[44] Third, results could be due to a survival effect. However, it is unlikely that individuals with a combination of brain atrophy and high BMI had higher survival than individuals without these characteristics. Fourth, cerebral atrophy occurs naturally with aging and therefore in individuals in whom there is no evidence of cognitive decline. This is evidenced in our study, where 94% of the participants had an MMSE score of ≥26 (88% had a score of ≥27), and only 11 women were demented. Thus, the clinical significance of this finding may be viewed as uncertain.

The epidemic of obesity that is being observed in aging Western societies presents a serious public

health problem and, based on our new findings, has far-reaching implications. If overweight and obesity contribute not only to diseases of middle age but also to degenerative diseases of late life, the health ramifications of excess body fat will stress healthcare systems for many years to come. Given the myriad of risk factors that preclude cerebrovascular events in the elderly, it appears that obesity is yet another factor that should be actively intervened upon to reduce diseases of advanced aging, such as cerebral degeneration and dementia.

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