Relationship Between Body Mass Index and Gray Matter Volume in 1,428 Healthy Individuals

Yasuyuki Taki[1], Shigeo Kinomura[1], Kazunori Sato[1], Kentaro Inoue[1], Ryoi Goto[1], Ken Okada[1], Shinya Uchida[1], Ryuta Kawashima[2] and Hiroshi Fukuda[1]

Objective: To investigate any correlation between BMI and brain gray matter volume, we analyzed 1,428 healthy Japanese subjects by applying volumetric analysis and voxel-based morphometry (VBM) using brain magnetic resonance (MR) imaging, which enables a global analysis of brain structure without *a priori* identification of a region of interest.

Methods and Procedures: We collected brain MR images from 690 men and 738 women, and their height, weight, and other clinical information. The collected images were automatically normalized into a common standard space for an objective assessment of neuroanatomical correlations in volumetric analysis and VBM with BMI.

Results: Volumetric analysis revealed a significant negative correlation in men ($P < 0.001$, adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus), although not in women, between BMI and the gray matter ratio, which represents the percentage of gray matter volume in the intracranial volume. VBM revealed that, in men, the regional gray matter volume of the bilateral medial temporal lobes, anterior lobe of the cerebellum, occipital lobe, frontal lobe, precuneus, and midbrain showed significant negative correlations with BMI, while those of the bilateral inferior frontal gyri, posterior lobe of the cerebellum, frontal lobes, temporal lobes, thalami, and caudate heads showed significant positive correlations with BMI.

Discussion: Global loss and regional alterations in gray matter volume occur in obese male subjects, suggesting that male subjects with a high BMI are at greater risk for future declines in cognition or other brain functions.

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INTRODUCTION

Obesity has been associated with hypertension (1–3), coronary heart disease (4), and diabetes mellitus (5). In addition, obesity has also been found to be associated with poor cognitive function (6,7) and has come to the forefront as a risk factor for Alzheimer's disease (AD) (8–10). Since AD (11–14) and several cerebrovascular risk factors, such as hypertension and elevated systolic blood pressure (15,16), are associated with brain volume decreases, obesity may be associated with brain volume decreases.

BMI is one of the most commonly used indices of obesity. A recent population-based study investigated the relationship between BMI and cerebral atrophy of the four major brain lobes in middle-aged women using computed tomography (17). The study revealed that women with atrophy of the temporal lobe had higher BMIs at each examination year than did women without temporal lobe atrophy in a cross-sectional analysis, and also revealed that BMI was a predictor for temporal lobe atrophy in a longitudinal analysis. In addition, a cross-sectional study investigated the correlation between BMI and global brain volume in middle-aged men and women, using magnetic resonance (MR) imaging (18). Elevated BMI was associated with reduced global brain volume. More recently, a comparison of regional gray matter volume between 24 obese and 36 lean white individuals was conducted applying voxel-based morphometry (VBM) (19). VBM, an established automated neuroimaging technique, enables the global analysis of brain structure without *a priori* identification of a region of interest (20). It is not biased towards any specific brain region and permits the identification of unsuspected potential brain structural abnormalities. The VBM-based study revealed that the regional gray matter volume of the postcentral gyrus, frontal operculum, putamen, and the middle frontal gyrus of obese individuals was significantly lower than in lean individuals.

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[1]Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer (IDAC), Tohoku University, Sendai, Japan; [2]Department of Functional Brain Imaging, IDAC, Tohoku University, Sendai, Japan. Correspondence: Yasuyuki Taki (ytaki@idac.tohoku.ac.jp)

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Although these studies have shed light on the relationship between BMI and brain structural abnormalities, gender differences have not been clarified. Moreover, it has not been clarified whether the findings of the VBM-based study in whites (19) are applicable to the Japanese, because most Japanese are not overtly obese, despite a high prevalence of obesity-related problems (21), suggesting that the Japanese as a race may be more vulnerable to obesity than whites.

The present study examined the correlation between BMI and gray matter volume, using brain MR images of 690 healthy Japanese men and 738 healthy Japanese women. To accomplish this, we first estimated the correlation between BMI and global gray matter volume, by applying a volumetric analysis using the gray matter ratio in men and women. Next, we estimated the correlation between BMI and regional gray matter volume by applying VBM in men and women.

METHODS AND PROCEDURES

Subjects

Written informed consent was obtained from each subject after a full explanation of the purpose and procedures of the study, according to the declaration of Helsinki (1991), prior to MR image scanning. Approval for these experiments was obtained from the institutional review board of Tohoku University.

All of the subjects were Japanese individuals recruited for the Aoba Brain Imaging Project in Sendai, Japan. The Aoba Brain Imaging Project was conducted to create a database of normal Japanese brain images (22). We announced the purpose of our study using several kinds of mass media, and we collected volunteers who called our project center to state their interest in participating. During a preliminary telephone interview, we excluded those with a past or present history of any malignant tumor, head trauma, cerebrovascular disease, epilepsy, or any psychiatric disease. Prior to the acquisition of brain MR images, medical doctors interviewed the subjects to obtain clinical information. Subjects with previous histories or symptoms of a central nervous system disease of any kind or brain injury were excluded from the study, using information obtained during the interview. We collected brain MR images from 1,637 subjects in the Aoba Brain Imaging Project. Radiologists inspected all MR images, and images with brain tumors of any kind, major infarctions (except lacunar infarction), and hemorrhages (observed as low intensity areas in T2-weighted images), were excluded. In addition, we excluded incomplete data sets from the collected data. Thus, we analyzed brain images from 1,428 subjects for the study, consisting of 690 men and 738 women. The height and weight of each subject were obtained by a self-administered questionnaire. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. The BMI data were used in the subsequent analyses as discrete variables as follows: 0 (underweight: BMI <20 kg/m^2), 1 (within normal range: BMI 20–24.9 kg/m^2), 2 (overweight: BMI 25–29.9 kg/m^2), and 3 (obesity: BMI ≥30 kg/m^2). Blood pressure in the right brachial artery was measured in the sitting position after a 10-min rest.

Image acquisition

Brain MR images from each subject were taken using the same 0.5-T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with two different pulse sequences: (i) 124 contiguous, 1.5 mm–thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in steady state: repetition time, 40 ms; echo time, 7 ms; flip angle, 30; voxel size, $1.02 \times 1.02 \times 1.5$ mm^3), and (ii) 63 contiguous, 3 mm-thick axial planes of gapless (using interleave) proton probability density weighted images/T2-weighted images (dual echo fast spin echo: repetition time, 2,860 ms; echo time, 15/120 ms; voxel size, $1.02 \times 1.02 \times 3$ mm^3). T1-weighted images were used for image analyses. Probability density–weighted images/T2-weighted images were used for clinical evaluations.

Image analysis of volumetric analysis

After image acquisition, all T1-weighted MR images were analyzed using the Statistical Parametric Mapping 2 (SPM2) software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/) (23) in MATLAB (MathWorks, Natick, MA). First, T1-weighted MR images were transformed to the same stereotactic space by registering each of the images to the same template image. The template image we used was the International Consortium for Brain Mapping 152 template (Montreal Neurological Institute), which was derived from 152 normal subjects and approximates the Talairach space (24). This process is called linear normalization. Then, tissue segmentation from the raw images to the gray matter, white matter, cerebrospinal fluid space, and non-brain tissue segments was performed, using the SPM2 default segmentation procedure. We applied these processes using the MATLAB file "cg_vbm_optimized" (http://dbm.neuro.uni-jena.de/vbm.html). The voxel values of each segmented image consisted not of binary (i.e., 0 or 1), but 256-grade (i.e., between 0/255 and 255/255) signal intensities, according to their tissue probability. The linear-normalized, segmented images were restored to the native space to determine the volume of each segment. The actual volumes of the entire normalized, segmented, and restored segmented images were determined by adding the voxel volumes (1 mm^3), multiplying by each voxel value and dividing by 255. To normalize the head size of each subject, we defined the "gray matter ratio" as the percentage of the gray matter volume divided by the intracranial volume, to normalize differences in head size. Intracranial volume was determined by adding the gray matter, white matter, and cerebrospinal fluid space volumes. A volumetric analysis using the gray matter ratio was then applied to estimate the global gray matter volume (16,25).

Image analysis of VBM

All T1-weighted MR images were analyzed using SPM2. First, T1-weighted whole brain structural MR images of each subject were transformed to the same stereotactic space by registering each of the images to the same template image using a 12-parameter affine transformation (26), similar to the first process of the volumetric analysis. Then, tissue segmentation from the transformed images to the gray matter, white matter, cerebrospinal fluid space, and non-brain tissue segments was performed using the SPM2 default segmentation procedure. Next, the segmented gray matter images were nonlinearly normalized to the gray matter template of SPM2 using $7 \times 8 \times 7$ nonlinear basis functions in the three orthogonal directions. These normalization parameters were reapplied to the T1-weighted whole brain structural images of each subject for performing spatial optimal normalization. The optimally normalized T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid space. The normalized, segmented gray matter images were then modulated by calculating the Jacobian determinants derived from the special normalization step, and multiplying each voxel by the relative change in volume, as in the method of Good *et al.* (27). This modulation step was performed to correct for volume changes in the nonlinear normalization. The normalized, segmented, and modulated gray matter images were smoothened by convoluting a 12 mm–full width at half maximum isotropic Gaussian kernel. This smoothening step was applied to remove individual variations in gyral anatomy and to render data more normally distributed, according to the central limit theorem.

Statistical analyses of the volumetric analysis and VBM

In the volumetric analysis, a general linear model was used to investigate the main effect of BMI, adjusting for age, gender, lifetime alcohol intake, history of hypertension, and diabetes mellitus, and the BMI × gender interaction on the gray matter ratio. In addition, partial correlation coefficients and statistical significance between BMI and the gray matter

Table 1 Characteristics of the subjects

	Men (n = 690)		Women (n = 738)		
	Mean (s.d.)	Range	Mean (s.d.)	Range	P
Age (years)	44.5 (16.1)	12–81	46.4 (14.1)	12–80	0.020
Height (cm)	168.3 (6.28)	149–187	155.8 (5.37)	136–171	<0.001
Weight (kg)	66.3 (9.57)	37–130	53.9 (7.26)	38–91	<0.001
BMI (kg/m^2)	23.41 (3.00)	13.2–40.1	22.23 (2.97)	15.2–33.3	<0.001
Systolic BP (mm Hg)	129.2 (16.5)	80–220	124.9 (17.8)	70–190	<0.001
Diastolic BP (mm Hg)	78.7 (11.2)	50–120	74.9 (12.0)	48–130	<0.001
Lifetime alcohol intake (kg)	181.0 (389.3)	0–4,663	0.75 (3.25)	0–33.5	<0.001

ratio, after adjusting for age, history of hypertension, and diabetes mellitus, were calculated for each gender. In the volumetric analysis, we set the significance level at $P < 0.05$. In the VBM analysis, smoothened gray matter images were used for statistical analyses using SPM2. To investigate the correlation between BMI and the regional gray matter volume, multiple regression analysis was performed. BMI, age, lifetime alcohol intake, history of hypertension, and diabetes mellitus were used as independent variables, and regional gray matter volume as a dependent variable in each gender. We set the significance level at $P < 0.05$ for the family-wise error rate. The results of SPM image analysis were superimposed onto a structural MR image, which was the average image of all of the subjects' normalized segmented gray matter images, to facilitate correlation with anatomic structures.

RESULTS

Subject characteristics

Figure 1 shows the distribution of BMI in each gender. The subject characteristics are shown in **Table 1**, and clinical information is shown in **Table 2**. As shown in **Table 1**, there were significant differences between men and women with regard to BMI, age, and cerebrovascular risk factors. Therefore, first we checked the main effect of BMI and the BMI × gender interaction on the gray matter ratio adjusting for age, gender, lifetime alcohol intake, history of hypertension, and diabetes mellitus in the subsequent volumetric analysis.

Volumetric analysis: correlation between BMI and gray matter ratio

There was a significant main effect of BMI on the gray matter ratio adjusting for age, gender, lifetime alcohol intake, history of hypertension, and diabetes mellitus (*F* ratio, 8.139; $P < 0.001$), and the BMI × gender interaction adjusting for age, gender, lifetime alcohol intake, history of hypertension, and diabetes mellitus (*F* ratio, 6.138; $P < 0.001$) on the gray matter ratio. Since there was a significant BMI × gender interaction on the gray matter ratio, we decomposed the interaction and calculated the partial correlation coefficient between the gray matter ratio and BMI in each gender separately. There was a significant negative correlation between BMI and the gray matter ratio in men, after adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus (partial correlation coefficient, −0.187, $P < 0.001$), while there was no significant correlation between BMI and the gray matter ratio in women, after adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus (partial correlation coefficient, 0.009, $P = 0.813$).

Table 2 Clinical information on the subject

	Men (n = 690)	Women (n = 738)	
	n (%)	n (%)	P
Prevalence of obesity			
25 ≤ BMI < 30	163 (23.6)	110 (14.9)	<0.001
30 ≤ BMI	15 (2.2)	12 (1.6)	0.448
Hypertension	95 (13.8)	71 (9.6)	0.015
Diabetes mellitus	26 (3.8)	12 (1.6)	0.012
Hypercholesterolemia	42 (6.1)	71 (9.6)	0.013
Ischemic heart disease	8 (1.2)	6 (0.8)	0.507
Arrhythmia	16 (2.3)	18 (2.4)	0.882

Table 3 Gray matter regions and coordinates of Talairach space of local maxima, showing significant negative correlation with BMI in men

Location	R/L	x	y	z	t	P
Uncus	L	−20	−19	−32	6.44	<0.001
	R	24	−18	−32	5.84	<0.001
	R	23	−42	−32	5.50	<0.001
	L	−49	−33	−31	5.00	0.002
	L	−25	−41	−34	4.99	0.002
	R	56	−39	−28	4.59	0.010
Cerebellum (anterior lobe)	L	−7	−41	−30	4.45	0.018
	R	50	−36	−30	4.26	0.039
	L	−10	−43	−29	4.21	0.046
	R	32	−88	−20	5.38	<0.001
Fusiform gyrus	L	−17	−93	−20	4.53	0.013
Superior parietal lobule	R	25	−74	−45	5.07	0.001
Precentral gyrus	R	40	3	31	5.06	0.001
Inferior frontal gyrus	R	23	26	−25	4.94	0.002
Precuneus	L	−22	22	−26	4.71	0.006
	R	24	−78	41	4.71	0.006
	R	11	−62	43	4.58	0.011
	R	17	−76	46	4.39	0.023
	L	−13	−74	45	4.36	0.026
Superior frontal gyrus	R	11	48	40	4.62	0.009
	L	−14	44	42	4.46	0.017
Midbrain	R	3	−31	−15	4.58	0.011

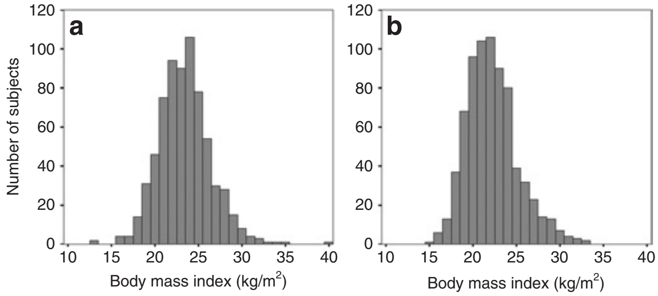

Figure 1 Distribution of BMI in (**a**) male and (**b**) female subjects.

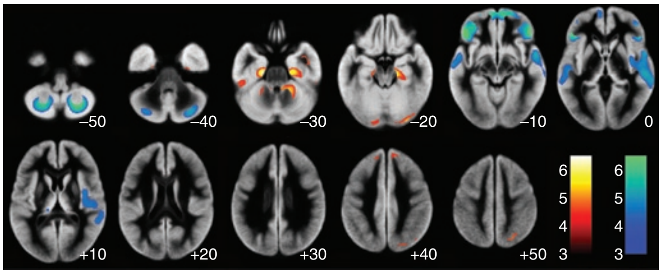

Figure 2 Gray matter regions that show significant negative (red scale) and positive (blue scale) correlations with BMI in men. The left side of the image represents the left side of the brain. Color scales indicate *t*-scores. The number at the bottom of the right side of each image indicates the value of the *z*-axis in Talairach stereotaxic space.

Table 4 Gray matter regions and coordinate of Talairach space of local, maxima showing significant positive correlation with BMI in men

Location	R/L	*x*	*y*	*z*	*t*	*P*
Inferior frontal gyrus	L	−46	32	−6	7.14	<0.001
	R	49	37	−9	6.75	<0.001
	L	−48	37	5	4.46	0.018
Cerebellum (posterior lobe)	R	25	−65	−50	6.53	<0.001
	L	−26	−66	−49	6.10	<0.001
Superior frontal gyrus	R	9	62	−9	6.21	<0.001
Superior temporal gyrus	R	57	2	−6	5.52	<0.001
Middle temporal gyrus	L	−61	−11	−10	4.86	0.003
Thalamus (pulvinar)	L	−15	−30	10	4.55	0.012
	R	14	−32	8	4.20	0.047
	R	15	−29	10	4.26	0.038
	R	16	−32	7	4.20	0.048
Cingulate gyrus	R	22	−61	6	4.48	0.016
Caudate head	L	−10	15	3	4.43	0.019
	R	10	13	4	4.19	0.049
Inferior temporal gyrus	R	67	−14	−13	4.20	0.047
Precentral gyrus	L	−56	5	7	4.20	0.047

VBM: correlation between BMI and regional gray matter volume

Since there was a significant BMI × gender interaction with the gray matter ratio, we analyzed the correlation between BMI and the regional gray matter volume in each gender separately. In men, the regional gray matter volume of the bilateral medial aspects of the temporal lobe, bilateral anterior lobes of the cerebellum, bilateral fusiform gyrus, bilateral frontal lobes, bilateral precuneus, and midbrain showed significant negative correlations with BMI, after adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus (red scale in Figure 2, Table 3). In addition, the regional gray matter volume of the bilateral inferior frontal gyri, bilateral posterior lobe of the cerebellum, bilateral frontal and temporal lobes, bilateral thalami, and bilateral caudate heads showed significant positive correlations with BMI, after adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus in men (blue scale in Figure 2, Table 4). In women, no gray matter region showed a significant negative or positive correlation with BMI.

DISCUSSION

We have shown a relationship between BMI and both global and regional gray matter volumes measured in a large number of healthy Japanese subjects. There was a significant BMI × gender interaction on the gray matter ratio adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus. In men, BMI showed significant negative correlations with the gray matter ratio, suggesting that elevated BMI is associated with global gray matter volume reduction. In addition, in men, BMI showed significant negative correlations with the regional gray matter volume of several regions. However, BMI also showed significant positive correlations in some other regions, suggesting that regional alterations in gray matter volume occur in male subjects with a high BMI. Although regional increases in gray matter volume as well as regional decreases were found, global gray matter volume decreased with increasing BMI in men with a high BMI. In women, there was no significant correlation between BMI and global or regional gray matter volume.

In men, BMI showed a significant negative correlation with global and regional gray matter volume, after adjusting for age, lifetime alcohol intake, history of hypertension, and diabetes mellitus. Several mechanisms may be involved in these obesity-related abnormalities in brain morphology. Age-related neuronal loss appears to be accelerated by a number of vascular factors that increase ischemia (28,29), and obesity has been related to ischemia and to a variety of vascular pathologies that are also potentially related to atrophy, including carotid artery wall thickening (30), vascular and coronary endothelial dysfunction (31–33), peripheral resistance, arterial stiffness (34), and ventricular hypertrophy. In addition, obesity may increase cortisol secretion (35), which may lead to a brain volume decrease (36). These findings may account for direct and indirect biologically plausible mechanisms explaining the relationship between a high BMI and the decrease in gray matter volume.

In contrast to men, there was no significant correlation between BMI and global or regional gray matter volume in women. The pattern of fat distribution differs between men and women, with visceral fat predominating in men and subcutaneous fat predominating in women (37). Visceral fat accumulation is more closely related to metabolic syndromes than subcutaneous fat accumulation (38,39). We think the difference in the findings between men and women may be the result of the differences in fat distribution. To investigate this further, measurements of body fat patterning would be needed, e.g., by applying the waist-to-hip ratio.

There were significant negative correlations between BMI and regional gray matter volume in the bilateral medial temporal lobe, occipital lobe, frontal lobe, and the anterior lobe of the cerebellum in men. However, our results do not agree with a VBM-based study that showed significant negative correlations between obesity and the regional gray matter volume in the postcentral gyrus, frontal operculum, putamen, and middle frontal gyrus (19). There are several possible reasons for the differences. First, 1,428 subjects participated in our study, whereas the VBM-based study involved only 24, suggesting that our study had much higher statistical power. Second, we analyzed men and women separately, because of the different patterns of fat distribution. Third, race-related differences may account for the different results, because most Japanese are not overtly obese, despite the high prevalence of obesity-related problems (21). suggesting that the Japanese, as a race, may be more vulnerable to obesity than whites.

In men, regional gray matter volume in the bilateral medial aspect of the temporal lobe, including the hippocampus, showed a significant negative correlation with BMI, after adjustment for age, and lifetime alcohol intake, history of hypertension, and diabetes mellitus. A population-based study revealed that women with atrophy of the temporal lobe had higher BMIs, and also revealed that BMI was a predictor for temporal lobe atrophy in a longitudinal analysis (17). In addition, obesity in middle age is associated with an increased risk of dementia and AD in later life (6,8–10). Moreover, several neuroimaging studies have revealed that patients with AD show significantly smaller volumes of the medial temporal lobes, including the hippocampus, than do normal elderly (12–14). Although the mechanisms of the correlation between obesity and decrease of hippocampal gray matter volume are unclear, there are relationships between obesity and hypercortisolism (40), and higher cortisol levels in relation to lower hippocampal volumes have been observed in AD (41). Given these findings, the relationship between obesity and AD may be derived from the findings of the present study, which showed a significant negative correlation between regional gray matter volume of the bilateral hippocampus and BMI.

A significant positive correlation between BMI and regional gray matter volume of the posterior lobe of the cerebellum, perisylvian regions of the bilateral frontal and temporal lobes, and bilateral orbitofrontal gyri was found in men. Although we have not clarified the mechanisms, a VBM-based study also revealed that obese individuals showed significant larger regional gray matter volume in the left calcarine cortex, left middle occipital gyrus, left inferior frontal gyrus, and right cuneus than did lean individuals, suggesting that there are also significant increases in regional gray matter volume in obesity (19). Further studies are needed to examine this positive correlation between BMI and regional gray matter volume.

There are several limitations to the present study. First, it is a cross-sectional study. Thus, we have shown a relationship between BMI and gray matter volume, but we cannot clarify the causation between the BMI and gray matter volume. Second, because we obtained data on height and weight by self-questionnaire, we cannot rule out the possibility that there may be discrepancies in this data. One study examined the validity of self-reported height and weight compared with their measurement in a Japanese workplace population (42), and concluded that self-reported heights and weights were generally reliable in middle-aged, employed Japanese men and women. However the study also concluded that self-reported weight was biased by actual BMI, because subjects with higher BMIs significantly underestimated their weights, compared with those with smaller BMIs. Thus, there is a possibility that the correlations between BMI and global and regional gray matter volume were actually underestimated. Third, while we applied BMI as an indicator of obesity, we did not apply other measurements, such as waist-to-hip ratio. Although BMI measurements are widely used, BMI does not take into account body fat patterning, as does the waist-to-hip ratio. Further studies are needed to examine the correlation between body fat patterning and brain volume, for example, by applying the waist-to-hip ratio. Fourth, to examine whether the BMI was associated with the gray matter volume in both the volumetric analysis and VBM, we adjusted for lifetime alcohol intake, history of hypertension, and diabetes mellitus, because these factors are associated with regional gray matter volume (15,16,25,43). However, we cannot rule out other confounding factors that might affect the correlation between BMI and the gray matter volume. Fifth, we recruited the subjects by announcing the purpose of our study in the mass media; therefore, there may be some selection bias, such as health status. In addition, this bias may affect the result of gender differences seen in this study. Therefore, the results should be interpreted with caution.

In conclusion, we have shown a relationship between BMI and both global and regional gray matter volume in 1,428 healthy individuals. We showed that global gray matter volume loss and regional alterations in gray matter structures occur in male subjects with a high BMI. Our findings have important public health implications, because they suggest that male subjects with a high BMI may potentially be at greater risk for future declines in cognition or other brain functions.

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DISCLOSURE

The authors declared no conflict of interest.

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