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Gain in Adiposity Across 15 Years is Associated With Reduced Gray Matter Volume in Healthy Women

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Abstract

Objective—To test whether current gray matter volume (GMV) covaried with previously obtained longitudinal measures of weight gain—as assessed by increases in body mass index (BMI)—among otherwise healthy postmenopausal women. Cross-sectional results indicate that reduced GMV may be associated with excess body weight.

Methods—Demographic, biometric, and behavioral measures were obtained from 48 women as part of the Pittsburgh Healthy Women Study, a longitudinal epidemiological investigation initiated between 1983 and 1984. In 2005 and 2006, these women took part in a brain imaging protocol.

Results—Premenopausal BMI and a priori chosen confounding variables, including the number of years post menopause, an aggregate measure of perceived life stress spanning a 20-year period, resting blood pressure, total cerebral volume, and severity of white matter hyperintensities (a suspected indicator of aging-related silent cerebrovascular disease), explained ~22% of variance in total GMV. An additional 15% of the variance was uniquely explained by the change in BMI between pre- and postmenopausal longitudinal assessments, such that an increase in BMI predicted a greater reduction in GMV.

Conclusions—An increase in BMI during the menopausal transition and beyond is associated with reduced GMV among otherwise healthy women.

Keywords

body mass index; gray matter volume; menopause; weight gain

INTRODUCTION

The accelerated increase in obesity over the past two decades (1) has drawn attention to the effect of body weight not only on cardiovascular disease risk (2) and other health-related outcomes specific to peripheral target organ systems but also on the brain (3–6). In point, decreased brain gray matter volume (GMV) has been associated with obesity among community samples (7) and patients with Alzheimer's disease (8). Further, decreased hippocampal volume has been associated with a greater body mass index (BMI) and fat

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distribution among elderly individuals (9). Volumetric differences in the gray matter of other brain areas have also been associated with indicators of body weight and fat among otherwise healthy individuals who are lean and obese (10). Changes in white matter brain tissue are also associated with weight gain (11,12). For example, prior reports demonstrated that the integrity of white matter fiber tracts in the frontal lobes is reduced in obese individuals compared with their lean counterparts (11,13).

Metabolic factors may explain the associations between body weight and alterations in brain tissue, such as brain tissue volume. More precisely, the brain relies on constant metabolic substrate delivery and constant tissue oxygenation, rendering brain tissue especially vulnerable to changes in vascular function. In this regard, increased body weight and obesity may affect brain tissue and morphology by influencing cellular vascular function and substrate delivery and promoting abnormal lipid metabolism and fat accumulation (11). These vascular and substrate delivery changes may, in turn, lead to alterations in indicators of brain tissue volume (7,10,11) and tract integrity (12,13) in association with excess body weight. Hence, from a public health perspective, it is important to consider the possibility that lifestyle interventions that control weight could plausibly protect against structural (and possibly functional) declines at the level of the brain. In a corollary extension of this notion, there is clinical evidence to suggest that severe malnutrition, as observed among individuals with eating disorders, is associated with decreased brain tissue volumes (14) and that these structural brain alterations reverse after long-term disorder remission (15).

Taken together, cumulative evidence has thus revealed a cross-sectional association between indicators of brain morphology, particularly brain tissue volume, and current body weight with plausible vascular-metabolic substrates. It remains uncertain, however, whether weight gain per se may have an independent contribution to normative variation in brain tissue volume. Such provisional evidence would further suggest that dysregulation of weight could influence brain tissue volume. BMI is widely accepted as a general indicator of adiposity (16). Using BMI as a proxy for adiposity, we thus explored whether the change in BMI between midadult and later life would predict total volumes of gray and white matter in later life. To answer this question, we used volumetric brain imaging data obtained from 48 healthy women who have been studied over a 20-year period as part of the epidemiological Pittsburgh Healthy Women Study (HWS).

METHODS

Participants

This study included 48 women studied as part of the Pittsburgh HWS (17). Details regarding sampling, exclusion criteria, and demographics for the cohort of 541 women who began the study in 1983 to 1984 are reported elsewhere (17). Participants were recruited in 1983 and 1984 and were eligible if they were between 42 and 50 years, not menopausal (had menstruated in the previous 3 months), were not receiving hormone replacement therapy, were not hypertensive (or on blood pressure-lowering medication), were not receiving psychotropic medication, antidiabetic or antilipemic medication, and were not receiving thyroid or replacement hormone therapy. In 2005 and 2006, a subsample of 50 eligible women were invited to participate in an ancillary brain imaging protocol. Women were ineligible for the brain imaging protocol if they had: (a) a history of cardiovascular or cerebrovascular disease; (b) a prior stroke or cerebrovascular incident; (c) claustrophobia; (d) Type I or II diabetes; (e) cancer; (f) a current or prior diagnosis of a neuropsychiatric disorder (including a mood disorder, dementia, or suspected Alzheimer's disease); (g) used psychotropic, hypertensive, or glucoregulatory medications currently or in the past; and (h) a metallic implant. Of the 464 active HWS participants in September 2005, 209 met one or more exclusion criteria; 71 were not interested in participating; 134 could not be contacted

or conveniently tested. Results reported herein are for 48 participants who did not differ in age or educational attainment from nonparticipants. Data were lost from 2 of the 50 women because they declined to participate in the full brain imaging protocol. The University of Pittsburgh Institutional Review Board granted study approval. We have previously reported associations between indicators of life stress and brain morphology and stress-related functional neural activation and blood pressure reactivity among this sample population (18,19). Participants provided their informed consent after receiving a study description. See Tables 1 and 2 for participant characteristics.

Study Measures and Assessments

Premenopausal women who entered the HWS received a cardiovascular risk factor and psychosocial evaluation and were reassessed approximately every 2 to 3 years, depending on the timing of their last menstrual period and use of hormone therapy. The measures that were collected at each time point included height and weight for BMI calculation. At each visit, height was measured barefoot, and weight was measured in light clothing with a calibrated scale. Potential confounding variables such as years since menopause at the time of the brain scanning protocol, resting systolic blood pressure, chronic perceived psychosocial stress, and white matter hyperintensities collected at the time of the brain imaging protocol were also included in the present analyses.

Brain Imaging Protocol

Brain magnetic resonance imaging (MRI) measures included quantitative volumetric measurements of total brain tissue volumes and visual ratings of white matter hyperintensities, which are taken as indicators of small cerebro-vascular disease that are detectable even in the absence of clinical neurological signs (20). MRI images used to derive these measures were acquired with a 3T Signa scanner (GE Medical Systems, Milwaukee, Wisconsin). Brain tissue volumes were derived from coronal images acquired with a T_1-weighted 3D spoiled gradient recalled (SPGR) acquisition sequence (time to echo (TE) = 5 ms; time to repetition (TR) = 25 ms; flip angle = 40°; number of excitations (NEX) = 1; 124 slices 1.5 mm thick; 0-mm spacing between slices; matrix size = 256 × 192 pixels; field of view (FOV) = 24 × 18 cm). White matter hyperintensities were assessed from axial images obtained with a T_2-weighted fast spin-echo inversion recovery (FSEIR) sequence (effective TE = 160 ms; TR = 10004 ms; time to inversion (TI) = 2250 ms; NEX = 2). FSEIR images were acquired in the plane of the anterior and posterior commissures (5-mm slice thickness; 1-mm spacing between slices; matrix size = 256 × 192 pixels; FOV = 20 × 20 cm).

Quantitative Brain Volume Measures

Total volumes of gray matter, white matter, and cerebrospinal fluid (CSF) were determined using a previously validated procedure (21–23), termed the “Automated Labeling Pathway” (ALP). This procedure involves the application of a nonlinear registration algorithm (24) to transform a template brain (Montreal Neurological Institute Colin27 template) into the native anatomical space of each individual’s brain. Specifically, after skull and scalp stripping (25), the images are segmented into gray matter, white matter, and CSF. The brain images are then intensity normalized to match the image intensity distributions of the template image. A fully deformable automatic algorithm (26) is then used to register the template image to the individual subjects’ brain images. Total GMV, white matter volume, and CSF volume (in mm^3) were estimated by summing all voxels classified as these tissue types, using Insight Segmentation and Registration Toolkit (ITK) (available at www.itk.org).

Assessment of White Matter Hyperintensities

MRI indicators of white matter hyperintensities in the periventricular and subcortical white matter areas are taken to reflect the presence of age-related ischemic lesions and they have been correlated with lower regional GMV in older adults (27). To estimate the severity of white matter hyperintensities, two readers graded films of the T_2-weighted FSEIR images by the protocol of the Cardiovascular Health Study (28). Both readers were blind to participant characteristics and the study purpose. Using an atlas of predefined visual standards, each reader graded the T_2 images for white matter with a 9-point scale anchored by 0 = minimal and 8 = extensive. As determined by intraclass correlation coefficients (ICCs), the readers showed high interrater agreement for periventricular white matter grades (ICC = 0.94) and subcortical white matter grades (ICC = 0.92). White matter grades were thus averaged across the two readers. Also, because rater-averaged periventricular and subcortical white matter grades were highly correlated (r = .92), these two grades were averaged to compute a composite indicator of white matter severity. Compared with population-based norms for older individuals (29), the present sample had minimal white matter grades (Table 1). Further, none of the participants showed signs of gross brain pathology or an undiagnosed prior stroke, as determined by consensus evaluations between our readers and a neuroradiologist.

Data Analysis

To test whether changes between pre- and postmenopausal BMI predicted GMV or white matter volume, we executed two-step hierarchical regression analyses (modeling GMV and white matter volume separately as dependent variables). In the first step, we entered all potential confounders selected on the basis of previous research, including the premenopausal BMI. In the second step, we added the postmenopausal BMI and examined the R^2 change. With this method, the residuals calculated by entering postmenopausal BMI adjusted for premenopausal BMI reflected the change in BMI. The set of step 1 confounding variables selected for the models were chosen on the basis of previous research and clinical reasoning. These included years since menopause measured at the time of the scan (30), resting systolic blood pressure at the time of the scan (31,32), a measure of chronic perceived psychosocial stress summed across assessments from the premenopausal evaluation to the most recent postmenopausal evaluation used in our prior report on these women (18), grade of white matter hyperintensities, total brain tissue volumes, and premenopausal BMI. Age was not included as a primary covariate because of its restricted variance in our sample (standard deviation (SD) = 1.32). Years postmenopause was included because of the overall purpose of the HWS was to study the effects of the menopausal transition on health. Moreover, studies have shown that estrogen therapy, if initiated in the early menopausal period, is protective against the age-related neuronal loss in postmenopausal women (33,34). Systolic blood pressure was selected because it is more reliable to assess than diastolic blood pressure and because it is a better predictor of cardiovascular morbidity in the elderly. We did not include smoking because only two subjects were current smokers. At the time of the scan, women also completed the Center for Epidemiologic Studies Depression Scale (CES-D) (35): none of the subjects exceeded the threshold of 16, which indicates suspected clinical depression. Further by study design (17), none of the women reported being treated for psychiatric syndromes or using psychotropic medications at study entry. The mean ± SD CES-D score at the time of the scan was 4.35 ± 3.02, and was not significantly correlated with whole brain GMV or white matter volume; CES-D score was unrelated to the percentage of variance explained by BMI change in the regression models. Therefore, depression was omitted from analyses.

Because there is controversy on whether white and gray volumes may depend on total brain size, we ran an exploratory hierarchical regression including a measure of total cerebral

volume derived from the sum of total gray, total white, and total CSF volumes. As we did not find any significant association between BMI change and total white matter volume in initial analyses, we only used total gray volume as a dependent variable for the exploratory analysis including total cerebral volume as an additional step 1 covariate.

RESULTS

Sample characteristics are shown in Tables 1 and 2. Only one woman showed a decrease in BMI between longitudinal assessments (−0.3 BMI points), whereas the remainder increased in BMI (mean change = 3.79; range = −0.3 to 12.89).

In the first set of analyses, wherein total gray volume was treated as the dependent variable, premenopausal BMI, years since menopause, resting systolic blood pressure, chronic perceived psychosocial stress, and white matter hyperintensities explained 22% of the variance (step 1 R^2 = .222, ΔF p = .078). In the second step, BMI change—defined as the residuals calculated by entering postmenopausal BMI adjusted for premenopausal BMI—explained an additional 15% of the variance (step 2 ΔR^2 = .155, ΔF p = .004; β= −0.592) (Table 3). Similar results (step 2 ΔR^2 = .089, ΔF p = .045; β = −0.509) were obtained using baseline weight and weight at the time of the scan (see Table 1 for weight changes description). Moreover, this association could not be explained by normative variation in total cerebral volume. Hence, in exploratory analyses, the association between BMI change and total gray volume remained significant after the inclusion of total cerebral volume to the set of step 1 covariates in the regression model (step 1 R^2 = .515; step 2 ΔR^2 = .063, F = 5.309, p = .027;β = −0.392) (Table 4).

When total white matter was treated as a dependent variable, the association with all step 1 covariates was not significant (R^2 = .117, ΔF p = .426). In step 2, BMI change defined as the residuals calculated by entering postmenopausal BMI adjusted for premenopausal BMI did not account for a significant change in the percentage of variance explained by the model (ΔR^2 = .048, ΔF p = .828; β= −0.051) (Table 5).

DISCUSSION

The present results demonstrate a relationship between GMV and the change in BMI between the pre- and postmenopausal years, spanning an approximate 20-year period in the present sample. As such, these results provide novel evidence that an increase in BMI during an important life transition (menopause) among women is uniquely associated with reduced gray matter, apart from current BMI and other potential confounders. We emphasize that the current results do not permit causal inferences. Hence, it may be that preexisting variation in GMV may contribute to weight gain and a corresponding increase in BMI over time. Although we cannot definitively exclude this possibility, we would expect that behavioral changes or changes in metabolic regulation leading to increased BMI over time would more likely be the consequence of structural (and hence, functional) abnormalities in specific brain regions involved in the regulation of body weight homeostasis. The result of reduced gray volume associated with increased BMI is particularly noteworthy considering that our subjects were healthy older women, with no history of cardiovascular or psychiatric disease and no current or past pharmacological treatment for a chronic medical condition or psychiatric disorder. Further, none of the participants met the threshold for obesity (BMI ≥ 30) at their midlife evaluation and the postmenopausal mean BMI was 27.1. Finally, all of these women underwent a natural (nonsurgical) menopause.

The mechanisms linking decreased whole brain gray volume to weight gain during the transition into menopause may involve numerous biological and even behavioral or lifestyle

factors. For example, vascular factors or metabolic abnormalities may affect substrate delivery to the brain. Both the transition to menopause and weight gain are independently associated with increased incidence of cardiovascular risk factors and cardiovascular diseases in women (17,36). In addition, metabolic disturbances associated with weight gain, such as Type 2 diabetes and altered peripheral insulin sensitivity, have been associated to brain volume changes (37–41). The subjects in this study were healthy and free of cardiovascular, cerebrovascular diseases, or diabetes; hence, any contribution of the pathophysiology of these diseases must occur at subclinical levels among the current women. It is possible that subtle metabolic alteration may take place even in the absence of threshold hypertension, diabetes, or dyslipidemia.

In addition, it is plausible that circulating inflammatory cytokines may mediate the effect of an increase in BMI related to the menopause on brain tissue volume. In this regard, it is noteworthy that adipocytes produce inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (42,43), and that obesity and overweight are associated with increased inflammatory cytokine levels (44). Further, there is recent evidence that higher circulating levels of the inflammatory cytokine, IL-6, are associated with reduced hippocampal volume among otherwise healthy men and women (45). The transition to menopause and aging in general are also associated to an increase of circulating cytokines (46). Increased circulating cytokines are linked to a variety of negative health outcomes in men and women across different age spans, including greater brain atrophy than expected for age (47) and poorer performance on cognitive tests of attention/working memory and executive function in healthy volunteers (48). Although the women in our study did not have clinical cardiovascular disease, it is possible that, in this otherwise healthy sample, weight gain during the menopausal transition promoted subtle modifications in glucose metabolism and cytokine production, which, in turn, affected brain morphology via peripheral to central pathways (49).

Behavioral and lifestyle factors associated with the transition into menopause may also play an important role in determining the increase in BMI. Menopause can presage important lifestyle changes, such as retirement from work, changes in family structure (children moving away), and changes in dietary and activity habits, which could lead to weight gain. Although we could not control for dietary changes or changes in physical activity, the measures of physical activity at the time of the scan were not associated with total gray volume (data not shown). We also had information about marital status at the time of the scan. We found no difference in current BMI or BMI change among women who were married or living with a partner, never married, divorced, or widowed (data omitted for brevity, available on request). Further, whereas the loss of a spouse among older women may trigger abrupt and considerable lifestyle changes leading to weight gain, only three women in our sample were widowed at the time of the scan—suggesting that this factor did not account for our findings. We have previously reported associations between indicators of chronic life stress and region-specific brain morphology in post menopause (18); higher level of chronic perceived stress were found to be associated with smaller right hippocampal volume, independent from total gray volume. Importantly, the effect of change in BMI was independent from chronic perceived stress in this study, suggesting that stress-related factors may not directly account for our current observations. In aggregate, the present study expands the knowledge about the correlates of brain morphology in healthy individuals by highlighting the association between prospectively measured weight changes and total GMV.

Our results suggest that weight gain is not associated with white matter volume. Although other studies (11) reported a relationship between increased BMI and increased regional white matter volume, to our knowledge, the extent to which BMI affects total white matter

volume has not been sufficiently explored. It is possible that only specific brain regions morphology (as opposed to total white volume) is affected by BMI changes or that changes in white matter volume become apparent as an individual approaches more marked changes in BMI compared with the women in this study.

Limitations that may affect the interpretation of these results need to be acknowledged. First, although we have longitudinal assessments of BMI, we only have one postmenopausal measurement of brain volumes. Therefore, conclusions about actual changes in total gray volume cannot be drawn; it is possible that those subjects who experience a greater increase in BMI had lower total GMV throughout their life. Second, despite the fact that we observed a wide range of weight changes across the years, none of the subjects were obese at the baseline assessment; therefore, our results cannot be generalized to those women who are obese throughout their life. The inclusion of only women may also limit the generalizability of our results: we do not know whether weight gain across the decades of life would show similar association with total GMVs in men. The narrow age range may also limit the generalizability of the results, in that it was not possible to compare brain volumes in younger versus older women.

In summary, our results suggest a cumulative increase of “risk” for weight-related volumetric brain tissue changes over the course of the menopausal transition in women. This cumulative burden of additional weight on brain volume was observed among otherwise healthy women. Weight gain and BMI are highly modifiable risk factors that may be targeted to prevent or slow the progression of potentially adverse age-related changes in brain morphology. Future research will need to investigate the regional specificity of the current findings. Women may be particularly motivated to maintain a healthy weight in the postmenopausal years, should it be confirmed that weight gain causes alteration in brain function that is important to quality of life.

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Glossary

BMI	body mass index
FOV	field of view
FWHM	full width at half-maximum
NEX	number of excitations
TE	time to echo
TI	time to inversion
TR	time to repetition

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TABLE 1

Age, BMI, and Menopausal Characteristics of the Sample (n = 48)

	Mean ± SD	Range
Age at MRI scan	67.98 ± 1.32	65–71
BMI at the time of the scan	27.13 ± 4.19	21.63–39.44
BMI at screening	23.33 ± 2.7	18.79–29.80
Change from screening to scan (BMI points)	3.79 ± 3.01	−0.30—12.89
Weight at the time of the scan	154.41 ± 21.91	104–211
Weight at screening	139.67 ± 20.85	100–207
Change in weight from screening to scan	16.23 ± 14.64	−6.50—65
Years post menopause	15.45 ± 2.48	10.37–19.67
Resting SBP (mm Hg)	125.45 ± 12.8	160–106.5
Resting DBP (mm Hg)	74.56 ± 6.8	58.5–88
Total gray matter volume	497523.18 ± 44297	404500–594470
White matter hyperintensity grade (0–8 scale)	1.91 ± 1.24	0.50–6.50

BMI = body mass index; SD = standard deviation; MRI = magnetic resonance imaging; SBP = systolic blood pressure; DBP = diastolic blood pressure.

TABLE 2

Socioeconomic Characteristics of the Subjects

	% (*n*)
Income (*n* = 40)	
>$50,000/year	57 (23)
Education (*n* = 45)	
High school or GED	20 (9)
Some college/vocational training	28.9 (13)
Bachelor's degree	20 (9)
Master's degree or higher	31.1 (14)
Hormone replacement therapy (*n* = 46)	
Current	17.4 (8)
Former	50 (23)
Never	32.6 (15)

GED = General Educational Development Test.

TABLE 3

Summary of the Two-Step Hierarchical Regression for the Variables Predicting Total Gray Matter Volume

	B	SE B	*β*	Sig.
Step 1				
Years post menopause	−6918.087	2642.12	−0.392	.013
Resting SBP	106.083	573.308	0.027	.854
Premenopausal BMI	−4761.170	2511.046	−0.281	.066
Chronic perceived psychosocial stress	−1609.046	2801.827	−0.086	.569
White matter hyperintensities	−5997.09	5177.019	−0.170	.254
Step 2				
Years post menopause	−6141.296	2410.104	−0.348	.015
Resting SBP	361.453	526.778	0.092	.497
Premenopausal BMI	2340.633	3267.260	0.138	.478
Chronic perceived psychosocial stress	929.099	2675.661	0.050	.730
White matter hyperintensities	−8726.863	4781.193	−0.248	.076
Current BMI	−6165.187	2033.638	−0.592	.004

Step 1 R^2 = .222; step 2 ΔR^2 = .155, F = 9.191, p = .004.

Sig. = significance; SBP = systolic blood pressure; BMI = body mass index.

TABLE 4

Summary of the Exploratory Hierarchical Regression, for the Variables Predicting Total Gray Matter Volume After Adjusting for Total Brain Volumes

	B	SE B	β	Sig.
Step 1				
Years post menopause	−2474.001	2312.333	−0.140	.292
Resting SBP	147.241	458.611	0.037	.750
Premenopausal BMI	−2780.643	2051.442	−0.164	.183
Chronic perceived psychosocial stress	−439.127	2254.474	−0.024	.847
White matter hyperintensities	−5220.235	4143.801	−0.148	.216
Total brain volumes	0.268	0.057	0.600	.000
Step 2				
Years post menopause	−2568.093	2188.796	−0.146	.248
Resting SBP	310.574	439.785	0.079	.485
Premenopausal BMI	1647.260	2731.774	0.097	.550
Chronic perceived psychosocial stress	1080.157	2233.222	0.058	.632
White matter hyperintensities	−7132.672	4008.608	−0.203	.084
Total brain volumes	0.232	0.056	0.518	.000
Current BMI	−4079.175	1770.405	−0.392	.027

Step 1 R^2 = 0.515; step 2 ΔR^2 = 0.062, F = 5.309, p = .027.

Sig. = significance; SBP = systolic blood pressure; BMI = body mass index.

TABLE 5

Summary of the Two-Step Hierarchical Regression for the Variables Predicting Total White Matter Volume

	B	SE B	β	Sig.
Step 1				
Years post menopause	−11442.7	5304.836	−0.344	.037
Resting SBP	−182.094	1151.086	−0.025	.875
Premenopausal BMI	−1405.54	5041.665	−0.044	.782
Chronic perceived psychosocial stress	−364.099	5625.494	−0.010	.949
White matter hyperintensities	338.859	10394	0.005	.974
Step 2				
Years post menopause	−11317.1	5403.197	−0.340	.043
Resting SBP	−140.8	1180.981	−0.019	.906
Premenopausal BMI	−257.161	7324.851	−0.008	.972
Chronic perceived psychosocial stress	46.326	5998.548	0.001	.994
White matter hyperintensities	−102.552	10718.927	−0.002	.992
Current BMI	−996.926	4559.199	−0.051	.828

Sig. = significance; SBP = systolic blood pressure; BMI = body mass index.