Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Longitudinal Changes in Fat Mass and the Hippocampus

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Objective: This study aimed to investigate cross-sectional and longitudinal associations between fat mass (i.e., body mass index [BMI], waist circumference [WC], and waist to hip ratio [WTHR]) and hippocampal volumes.

Methods: UK Biobank participants ($N = 20,395$) aged 40 to 70 years (mean follow-up = 7.66 years), were included and categorized into one of four groups, which represented their baseline fat mass status and trajectory of change by follow-up assessment: normal weight to overweight/obesity, overweight/obesity to normal weight (ON), normal weight stable (NS), or overweight/obesity stable (OS). Regression models used NS (WC < 80 cm in women and < 94 cm in men; WTHR < 0.85 in women and < 0.90 in men; BMI < 25 kg/m^2 in women and men) as the reference group. Hippocampal volumes were automatically segmented using the FMRIB Software Library.

Results: Compared with NS, OS (BMI: $B = -62.23$ [SE = 16.76]; WC: $B = -145.56$ [SE = 16.97]; WTHR: $B = -101.26$ [SE = 19.54]) and ON (BMI: $B = -61.1$ [SE = 30.3]; WC: $B = -93.77$ [SE = 24.96]; WTHR: $B = -69.92$ [SE = 26.22]) had significantly lower hippocampal volumes.

Conclusions: The detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

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Study Importance

What is already known?

- In addition to being associated with deleterious health and well-being outcomes, including type 2 diabetes mellitus, cancer, and cardiovascular disease, overweight BMI in midlife confers a 35% increased risk of developing Alzheimer disease compared with normal BMI.

What does this study add?

- Our findings indicate that the detrimental effects of overweight/obesity on the neurological health of individuals may extend beyond the duration of overweight/obesity itself.

How might these results change the focus of clinical practice?

- The clinical translation of our research findings is important to ensure that possible populations at risk for poor neurological health are not overlooked and that, instead, targeted intervention programs are developed to mitigate identified risks.

Introduction

The prevalence of overweight and obesity has accelerated in recent decades, with current global estimates indicating that the proportion of adults with body mass index (BMI) greater than 25 kg/m^2 (i.e., overweight) is one in three (1,2). These findings are of particular importance within the context of our globally aging population given that previous research has demonstrated that, in addition to being associated with several unfavorable health and well-being outcomes (including type 2 diabetes mellitus, cancer, and cardiovascular disease) (3), overweight BMI in midlife confers a 35% increased risk of developing Alzheimer disease compared with normal BMI (4).

The hippocampus is a brain region that is sensitive to changes, particularly in the early stages of neurodegeneration (5-7). Notably, the accumulation of fat tissue, particularly visceral fat (which is often prevalent in individuals with overweight/obesity), is known to be closely linked with elevated levels of proinflammatory cytokines (8-10), which are associated with smaller hippocampal volumes (11). In animal models, obesity in aging is associated with a heightened state of systemic inflammation, which exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus (12). These pathophysiological consequences of overweight/obesity have been closely linked with impaired hippocampal integrity in humans (11,13). Interestingly, a postmortem study of nondemented elderly individuals revealed that those with obesity had neuropathological hallmarks of Alzheimer disease, such as higher levels of hippocampal amyloid-β peptides, amyloid precursor protein, and hyperphosphorylated tau protein, compared with those without obesity (14). However, neuroimaging studies have revealed that the association between fat mass and hippocampal volume in adults of middle to early-old age has been less consistent, with studies reporting negative (15-18), positive (19), or no association (20-22). The heterogeneous results may be explained by

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the typical use of BMI, which does not precisely index changes in visceral fat and is inherently biased by the aging process (23). Therefore, other cost-effective, feasible, and useful clinical measures, including waist circumference (WC) and/or waist to hip ratio (WTHR), may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in WC and WTHR have not been adequately investigated in previous studies examining the relationship between fat mass and hippocampal volume (12,16-17,24).

In the current study, we aimed to rectify these shortcomings by investigating the associations of fat mass (i.e., BMI, WC, and WTHR) and changes in fat mass over time with hippocampal volumes in women and men of middle to early-old age. Secondary aims were to (1) determine whether these associations differed between measures of fat mass and (2) determine which measures of fat mass were most strongly associated with total body fat and visceral fat, as measured by the gold standard tool, dual-energy x-ray absorptiometry (DXA). It was hypothesized that any observed associations between fat mass and the hippocampus would be dependent on (1) baseline fat mass status (i.e., normal weight, overweight, or obesity), (2) the trajectory of change, and (3) the measure of fat mass used. It was predicted that individuals who were classified as having chronic overweight/obesity (and who thereby experience chronic, low-grade, systemic inflammation as well as other comorbidities) would have lower hippocampal volumes than those who progressed from normal weight to overweight/obesity categories or maintained their weight within the normal range. Furthermore, it was hypothesized that these results would be best represented by the fat mass measure that was most suited for indexing changes in visceral fat.

Methods

Participants

A total of 502,536 participants aged 37 to 73 years at baseline (2006-2010) from the UK Biobank study (25) were considered for inclusion. Participants were recruited from the National Health Service central registers. Of those considered, as a minimum requirement, only those who had completed a structural magnetic resonance imaging (MRI) scan ($n = 21{,}390$) and who had a measure for BMI, WC, and hip circumference (HC) at baseline and the follow-up assessment (2014+) were included ($n = 20{,}849$). After we excluded participants with neurological disorders (including stroke; $n = 256$), those who were underweight (BMI < 18.5; $n = 179$), and those with extreme obesity (BMI > 50; $n = 20$), 20,395 participants remained for analysis in the present study. None of the included participants had dementia. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (reference: 11/NW/0382). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Fat mass measures

BMI, WC, and WTHR were measured at baseline, the first follow-up assessment, and the second follow-up assessment (Figure 1). Trained staff used standardized procedures to obtain body size measurements. Participants were asked to remove shoes, socks, and heavy outer clothing before body weight was measured with the Tanita BC-418MA body composition analyzer and standing height was measured using a Seca 202 height measure. BMI was calculated as weight (in kilograms)/height (in meters squared). WC was measured with a Wessex non-stretchable sprung tape measure at the level of the umbilicus, whereas HC was measured at the widest point. WTHR was computed as WC (in centimeters)/HC (in centimeters). Total body fat and visceral fat were measured (for 4,482 and 4,431 participants, respectively) using a DXA device, specifically the GE Lunar iDXA.

Of the 20,395 participants included in the study, 5,080 had an additional follow-up measure of fat mass (Figure 1). For these participants, annual changes in fat mass were calculated with the formula:

$$y = B_0 + B_1 \text{follow up (years)},$$

where B_0 is the fat mass at each time point and B_1 is the annual change in fat mass.

For each measure of fat mass, participants were then categorized into one of four groups, which represented their baseline fat mass status and their trajectory of change by follow-up assessment: normal weight to overweight/obesity (NO), overweight/obesity to normal weight (ON), normal weight stable (NS), or overweight/obesity stable (OS). Standardized criteria from the International Diabetes Federation (26) and the World Health Organization (27,28) were used to classify normal and overweight/obesity groups. Specifically, BMI was ≥ 25 kg/m^2 for men and women with overweight/obesity and < 25 kg/m^2 for men and women with normal weight; WC was ≥ 80 cm and ≥ 94 cm for women and men with overweight/obesity, respectively, and < 80 cm and < 94 cm for women and men with normal weight, respectively; and WTHR was ≥ 0.85 and ≥ 0.90 for women and men with overweight/obesity, respectively, and < 0.85 and < 0.90 for women and men with normal weight, respectively.

Covariates

Covariates included sex, follow-up period, self-reported age, educational attainment, vascular/heart problems (i.e., heart attack, angina, or hypertension), and diabetes diagnosed by a doctor. Participants were classified as having hypertension if they were using blood pressure medication and were classified as having diabetes if they were using oral antidiabetic medication or insulin. Further covariates included self-reported physical activity (i.e., number of days per week spent doing at least 10 minutes of continuous vigorous activity), smoking status (i.e., ever or never), and frequency of alcohol intake.

Image acquisition

MRI scans were acquired at the second follow-up assessment (Figure 1). All participants were imaged across three imaging centers with identical scanners (3T Siemens Skyra, running VD13A SP4) using a 32-channel head coil (29). T1-weighted images were acquired in the sagittal orientation using a three-dimensional magnetization-prepared rapid acquisition gradient echo sequence over a duration of 5 minutes (resolution = 1 × 1 × 1 mm; field of view = 208 × 256 × 256 matrix) (29).

Segmentation and image analysis

Images were processed and analyzed by the UK Biobank imaging team using FMRIB Software Library version 6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard MRI analysis protocols has been reported elsewhere (29,30); however, we have included an overview of key steps. The UK Biobank processing pipeline included a linear and then a nonlinear registration to a 1-mm-resolution version of the MNI152 template. Automated tissue segmentation was conducted, and subcortical structures, such as the hippocampus, were modeled.

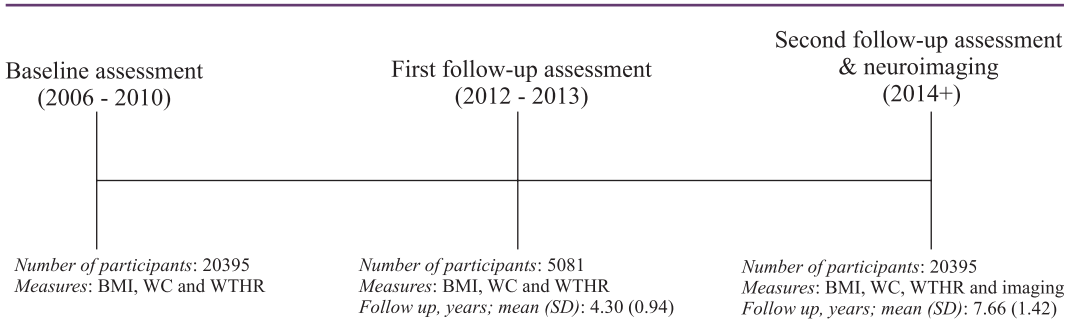

Figure 1 Timeline of UK Biobank study. WC, waist circumference; WTHR, waist to hip ratio.

Raw hippocampal volumes were multiplied by the overall volumetric head-size scaling factor to obtain normalized volumes, which were subsequently used for all analyses.

Statistical methods

All statistical analyses were conducted using R (version 3.6.1; R Foundation for Statistical Computing), in RStudio (version 1.1.419). Pearson correlation coefficients were used to measure the strength of the associations between BMI, WC, and WTHR and DXA measurements of total body fat and visceral fat. Multiple linear hierarchical regression models were then computed to quantify the association between fat mass and changes in fat mass and hippocampal volumes, controlling for age and sex (model 1). Model 2 further controlled for education, vascular/heart problems, diabetes, physical activity, smoking status, and alcohol use. Analyses investigating the associations between fat mass categories (i.e., NO, ON, NS, and OS) and the hippocampus also adjusted for length of follow-up (years). Within each fat mass category, longitudinal changes in fat mass and the hippocampus were assessed. Because the fat mass thresholds for categorization differed between men and women (particularly for WC and WTHR), these analyses were repeated separately. Both unstandardized beta coefficients and annual percentage change in fat mass were used in the reporting and interpretation of results, when appropriate. Annual percentage change was calculated by dividing the annual change in fat mass by the baseline fat mass and multiplying by 100. The α level was set at <0.05. Nonlinear associations were explored by fitting a squared term for fat mass. Assumptions of linearity, including homoscedasticity and normality of residuals, were examined.

Results

The participants' demographic and health characteristics are presented in Table 1. Differences between those who were included and excluded are reported in Supporting Information Table S1. For those included, participants were, on average, 54.86 years old (SD = 7.48 years) at baseline and had a mean follow-up time of 7.66 years (SD = 1.42 years). The average total hippocampal volume was 7,709.73 mm^3 (SD = 867.92 mm^3). On average, participants lost 68.6 g/y over the follow-up period. Box plots of fat mass change over the follow-up period between NS, NO, OS, and ON groups are presented in Figure 2. Demographic information for NS, NO, OS, and ON groups for each fat mass measure is presented in Supporting Information Tables S2-S4.

TABLE 1 Demographic and health characteristics

	Value
Sample size, *N*	20,395
Age, mean (SD), y	54.86 (7.48)
Follow-up period, mean (SD), y	7.66 (1.42)
Female sex, *n* (%)	10,658 (52.26)
BMI, mean (SD)	26.67 (4.16)
Waist circumference, mean (SD), cm	88.12 (12.44)
Waist to hip ratio, mean (SD)	0.86 (0.087)
Education (college degree), *n* (%)	9,491 (46.54)
Hypertension, *n* (%)	4,240 (20.79)
Diabetes, *n* (%)	544 (2.67)
Ever smoker, *n* (%)	11,623 (56.99)
Total hippocampal volume, mean (SD), mm^3	7,709.73 (867.92)

There were 109 (0.53%) participants missing data for education, 147 (0.72%) participants missing data for hypertension, 4 (0.02%) participants missing data for diabetes, and 44 (0.22%) participants missing data for smoking status.

Cross-sectional analyses revealed that after adjustment for all covariates, higher BMI, WC, and WTHR were each individually associated with lower hippocampal volumes (Supporting Information Table S5) (BMI: $B = -9.61$ [SE = 1.77]; WC: $B = -6.74$ [SE = 0.69]; WTHR: $B = -690.78$ [SE = 119.13]).

Overall, longitudinal changes in continuous BMI, WC, or WTHR were not significantly associated with lower hippocampal volumes (Supporting Information Table S6); however, compared with participants with NS, for BMI, WC, or WTHR, participants classified as OS (BMI: $B = -62.23$ [SE = 16.76]; WC: $B = -145.56$ [SE = 16.97]; WTHR: $B = -101.26$ [SE = 19.54]) or ON (BMI: $B = -61.1$ [SE = 30.3]; WC: $B = -93.77$ [SE = 24.96]; WTHR: $B = -69.92$ [SE = 26.22]) had significantly lower hippocampal volumes across all three measures of fat mass (Table 2). For WC or WTHR, participants with NO also had significantly lower hippocampal volumes than those with NS (WC: $B = -74.39$ [SE = 25.51]; WTHR: $B = -62.09$ [SE = 22.52]). However, for BMI, participants with NO had no significant difference in hippocampal volume compared with those with NS.

Analyses were repeated separately for women and men (Supporting Information Tables S7-S8). For men, OS (BMI: $B = -92.17$ [SE = 26.55];

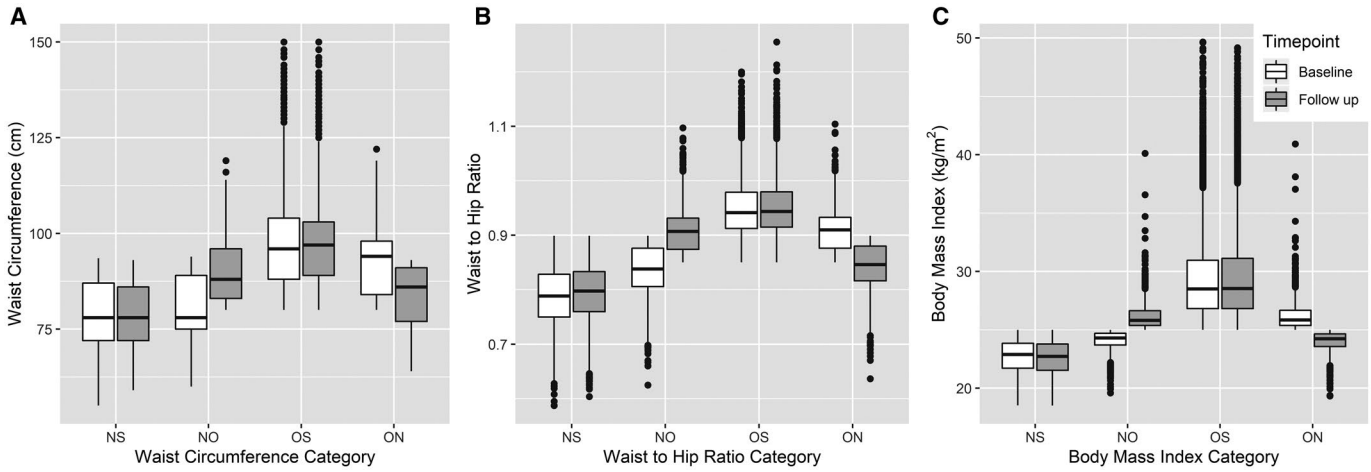

Figure 2 Fat mass change over follow-up for each group. (**A**) Waist circumference groups. (**B**) Waist to hip ratio groups. (**C**) BMI category groups. NO, normal weight to overweight/obesity; NS, normal weight stable; ON, overweight/obesity to normal weight; OS, overweight/obesity stable.

TABLE 2 Longitudinal categorical analysis results for total hippocampus

Measure	Predictors	Estimate	SE	95% CI	*P*	R^2
BMI	NO	−45.95	32.24	−109.14 to 17.25	0.154	0.155
	OS	−62.23	16.76	−95.07 to −29.38	**<0.001**	…
	ON	−61.10	30.30	−120.50 to −1.71	**0.044**	…
WC	NO	−74.39	25.51	−124.39 to −24.40	**0.004**	0.157
	OS	−145.56	16.97	−178.83 to −112.29	**<0.001**	…
	ON	−93.77	24.96	−142.69 to −44.85	**<0.001**	…
WTHR	NO	−62.09	22.52	−106.24 to −17.95	**0.006**	0.155
	OS	−101.26	19.54	−139.57 to −62.95	**<0.001**	…
	ON	−69.92	26.22	−121.32 to −18.53	**0.008**	…

Model adjusted for age, sex, follow-up (years), education, vascular/heart problems, diabetes, physical activity, smoking, and alcohol use. All estimates unstandardized for hippocampus (measured in cubic millimeters). $P < 0.05$ considered significant and presented in bold text.
NO, normal weight to overweight/obesity; ON, overweight/obesity to normal weight; OS, overweight/obesity stable; WC, waist circumference; WTHR, waist to hip ratio.

WC: $B = -206.02$ [SE = 25.69]; WTHR: $B = -114.98$ [SE = 29.08]) and ON (BMI: $B = -97.79$ [SE = 45.76]; WC: $B = -91.18$ [SE = 34.5]; WTHR: $B = -96.29$ [SE = 40.49]) groups were consistently associated with lower hippocampal volumes compared with the NS group across all measures of fat mass. However, no significant differences in hippocampal volumes were consistently found between the NO and NS groups. For women, the OS group had consistently lower hippocampal volumes than the NS group across all measures of fat mass (BMI: $B = -45.19$ [SE = 21.52]; WC: $B = -101.73$ [SE = 22.5]; WTHR: $B = -70.54$ [SE = 28.67]). For WC and WTHR, the NO group had lower hippocampal volumes than the NS group (WC: $B = -84$ [SE = 32.43]; WTHR: $B = -103.79$ [SE = 28.43]); however, these differences were not found for BMI. Participants with ON had significantly lower hippocampal volumes compared with the NS group for WC ($B = -113.16$ [SE = 36.51]); however, this difference was not observed for WTHR or BMI.

For each individual subgroup (NS, NO, OS, and ON), annual change in BMI, WC, or WTHR had no significant association with hippocampal volume (Supporting Information Table S9). This was consistently observed between women and men (Supporting Information Tables S10-S11).

As seen in Table 3, WC was most correlated with visceral fat ($r = 0.83$) compared with WTHR ($r = 0.73$) and BMI ($r = 0.69$). However, BMI was most correlated with total body fat ($r = 0.90$) compared with WC ($r = 0.72$) and WTHR ($r = 0.29$).

Discussion

In this study, we aimed to investigate the association of fat mass and longitudinal changes in fat mass with hippocampal volumes in women and men of middle to early-old age. To better understand these relationships, in the current study, we also aimed to determine whether observed associations differed between measures of fat mass and identify which measures of fat mass were most strongly associated with total body fat and visceral fat, as indicated by DXA. The key findings were

TABLE 3 Simple Pearson correlation analysis results between WC, WTHR, and BMI and DXA measures of TBF and VF

	TBF	95% CI	*P*	VF	95% CI	*P*
BMI	0.897	0.891-0.903	**<0.001**	0.688	0.672-0.703	**<0.001**
WC	0.719	0.706-0.734	**<0.001**	0.827	0.817-0.836	**<0.001**
WTHR	0.291	0.264-0.318	**<0.001**	0.728	0.714-0.742	**<0.001**

TBF and VF measured for 4,482 and 4,431 participants, respectively, using DXA. $P < 0.05$ considered significant and presented in bold text.
DXA, dual-energy x-ray absorptiometry; TBF, total body fat; VF, visceral fat; WC, waist circumference; WTHR, waist to hip ratio.

that (1) WC was most strongly correlated with visceral fat ($r=0.83$) compared with WTHR ($r=0.73$) and BMI ($r=0.69$), (2) individuals with chronic overweight/obesity had significantly lower hippocampal volumes (WC: 1.13% smaller; WTHR: 0.79% smaller; BMI: 0.49% smaller [after adjustment for all covariates]) compared with those who maintained a normal level of fat mass (WC < 80 cm in women and < 94 cm in men; WTHR < 0.85 in women and < 0.90 in men; BMI < 25 kg/m^2 in women and men) at baseline and follow-up (average follow-up = 7.66 years), and (3) individuals who were within a normal range of fat mass at the follow-up assessment, yet were previously classified as having overweight/obesity at baseline, had lower hippocampal volumes than those who remained at normal weight (WC: 0.73% smaller; WTHR: 0.55% smaller; BMI: 0.48% smaller [after adjustment for all covariates]). Notably, the significant cross-sectional association between fat mass and hippocampal volume was not previously detected in a study on the same cohort (18). In that particular study, the sample was half the size of the present study, and depression was also considered as a covariate. Our analysis did not include depression as a covariate, partly because of the significant degree of missingness present. The current findings emphasize the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

Overweight/obesity is a complex condition that has multifactorial components (including genetic, environmental, and socioeconomic factors) that underlie its etiology. The current findings further highlight the complexity of overweight/obesity by emphasizing the long-term impact the condition may have on the neurological health of individuals. There are several possible biological mechanisms that may explain the consistent finding that those with OS or ON had lower hippocampal volumes than those with NS across all measures of fat mass. For example, previous studies have demonstrated that the accumulation of fat tissue, particularly visceral fat, is closely linked with elevated levels of proinflammatory cytokines (19-21), which have been associated with smaller hippocampal volumes (22). This is of particular importance because the current results revealed that (1) WC was most strongly associated with visceral fat and (2) the largest effect was consistently found for WC, as those with OS and ON had 1.13% and 0.73% smaller hippocampal volumes, respectively, than those with NS for WC compared with WTHR (OS: 0.79% smaller hippocampus; ON: 0.55% smaller hippocampus) and BMI (OS: 0.49% smaller hippocampus; ON: 0.48% smaller hippocampus). Notably, no statistical differences between NS and NO groups were found for BMI, which was lowly correlated with visceral fat levels compared with WC but was most highly correlated with total body fat; however, for both WC and WTHR, the NO group had significantly lower hippocampal volumes than the NS group (0.58% and 0.49% smaller, respectively).

Taken together, the current findings seem to suggest that an accumulated burden of pathology may have developed in those with OS, ON, and NO, compared with NS, perhaps as a result of chronic, low-grade systemic inflammation that persists, which is common in individuals with overweight/obesity (because of an accumulation of visceral fat tissue), or other pathological mechanisms, resulting in lower hippocampal volumes. This is consistent with the literature, which has shown that chronic obesity is associated with a cascade of potentially harmful physiological processes (including oxidative stress, inflammation, and insulin resistance) implicated in the deterioration of metabolic homeostasis (31) and that chronic obesity has been linked with accelerated neurodegeneration (32). Furthermore, previous research has demonstrated that individuals who gained weight, lost weight, or maintained obesity had an increased risk of mortality compared with those who maintained normal amounts of body fat (33). Therefore, these results appear to indicate that it is the chronicity of overweight/obesity that is associated with lower hippocampal volumes. However, an alternative explanation is that, for reasons not well understood, those with ON or OS had lower hippocampal volumes at baseline. Although possible, this explanation is less likely given the substantial amount of evidence in the literature that has demonstrated the link between obesity and neurodegeneration (4,34,35), which also aligns with experimental data in animals showing that obesity in mice can lead to decreased neurogenesis and accelerated neurodegeneration, resulting in dementia pathology (36,37). Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present, and future research should investigate this further.

The use of BMI, WC, and WTHR enabled the comparison of results across three commonly used clinical measures/indices of fat mass. Although more precise technology for measuring fat mass exists, such as DXA and MRI (38), these tools require relatively large investments of time, money, and resources, compared with BMI, WC, and WTHR. Furthermore, longitudinal measures of fat mass, by using DXA or MRI, are currently not available in the UK Biobank data set. As a result, an important question is raised by these findings: which clinical measure (BMI, WC, or WTHR) best represents the association between fat mass and the hippocampus and which may, therefore, be a better predictor of future neurodegeneration? First, as previously noted, a correlation analysis indicated that WC was most strongly associated with visceral fat ($r=0.83$) compared with WTHR ($r=0.73$) and BMI ($r=0.69$). This may provide a theoretical rationale for its use as a clinical measure to assess the association between fat mass and the hippocampus. Furthermore, a subgroup analysis in women revealed statistically significant differences for WC between NO, OS, and ON groups and those with NS; however, these differences were not consistently found for WTHR and BMI (Supporting Information Table S7). Several possible reasons may account for these findings. For example, previous research has demonstrated that women tend to accumulate central fat (specifically visceral

fat) during midlife (39), which may explain the observed associations given that WC was most strongly correlated with visceral fat, which has been previously linked to neurodegeneration through the elevation of proinflammatory cytokines (22). Another possibility is that the individuals who were in each fat mass group (NS, NO, OS, and ON) varied to a certain degree between measures because of the differences in the standardized cutoff points used for categorization. Therefore, the observed differences in results may reflect the sensitivity of the fat mass thresholds for each category (NS, NO, OS, and ON) to better capture individuals who had healthier hippocampal volumes than others. To assess this, a post hoc analysis was conducted, in which a fifth group included individuals (n = 3,998) who consistently had NS for BMI, WC, and WTHR (henceforth consistent NS [CNS]). Interestingly, for WC, no difference was found between those with NS or CNS. Furthermore, the magnitude and significance of effects remained consistent between NS and NO, OS, and ON groups, with and without the inclusion of the CNS group (Supporting Information Table S12). Alternatively, for WTHR and BMI, the CNS group had significantly larger hippocampal volumes than those with NS. Furthermore, the differences between ON and OS groups and the NS group for BMI were no longer detected once the CNS group was included. A similar result was observed for the ON and NO groups for WTHR. Therefore, the CNS group was likely capturing the individuals with larger hippocampal volumes for BMI and WTHR but not WC. This may be because BMI and WTHR measures reflect body size and on-average head size, which is itself associated with hippocampal volume. These findings seem to further demonstrate the robustness and sensitivity of WC for assessing the relationship between visceral fat and hippocampal volume. Taken together, these results align with and extend on previous studies that have noted that WC is a more sensitive indicator for determining the adverse effects of overweight and obesity on brain health than BMI, particularly in women (40).

Key strengths of the current study include (1) the large cohort of adults of middle to early-old age (20,395 individuals) that included both men and women, (2) the use of longitudinal changes in fat mass, and (3) the use of multiple commonly used clinical measures/indices of fat mass (including BMI, WC, and WTHR) to address the questions of interest. Furthermore, because of the large sample size, a large number of relevant covariates could be adjusted for (including age, sex, follow-up period, educational attainment, vascular/heart problems [i.e., heart attack, angina, or hypertension], diabetes, physical activity, smoking status, and alcohol intake), which ensured that observed associations were unlikely driven by common comorbid conditions that are often associated with obesity, such as diabetes, hypertension, and physical activity levels. Notably, previous studies that have examined the association of longitudinal changes in fat mass with hippocampal volumes in adults of middle to early-old age have been limited by sample size (12,16,17). Two of the three studies used BMI as their only measure of fat mass (16,17); one was focused on a sample consisting only of men (16), whereas the other used self-reported BMI (12). The third estimated BMI and WC in participants aged 50 years (17). Given this, the current study is unique in its ability to directly measure, assess, and discuss the temporal association of longitudinal changes in BMI, WC, and WTHR with the hippocampus within a large cohort of both men and women.

A limitation of the current study is that imaging data were available only at one time point (Figure 1). Therefore, it is difficult to determine whether other age-related factors could be responsible for the observed differences or, as previously discussed, whether these differences were already present at baseline. For example, if smaller hippocampal volumes were observed at baseline and were associated with longitudinal increases in adiposity, then these findings may highlight a predisposed vulnerability to external food cues driving eating behavior. Furthermore, clear standardized thresholds for WC and WTHR that separate overweight and obesity groups do not currently exist. This limited the ability to identify possible differences that may exist between participants with overweight and obesity for WC and WTHR. Additionally, healthy participation bias for the UK Biobank cohort indicates that these findings may not be completely representative of the broader population and that they require replication in other data sets (41). Our study was limited to the association between changes in fat mass and the brain; however, future studies would benefit from investigating whether the observed results translate to differences in cognitive performance, particularly in domains related to the hippocampus such as learning and memory.

Conclusion

The current findings emphasize the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.O

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Supporting information: Additional Supporting Information may be found in the online version of this article.

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