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The Link Between Weight Gain and Hippocampal Atrophy in Bipolar Disorder: A Longitudinal Investigation in 934 Participants

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ABSTRACT

BACKGROUND: Obesity, which is common in bipolar disorder (BD), is associated with smaller hippocampal volumes. We do not know the role of weight/weight gain in relation to longitudinal hippocampal changes among individuals with BD.

METHODS: In collaboration with the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis)-BD Working Group, we obtained T1-weighted magnetic resonance imaging and clinical data from 233 participants with BD and 701 healthy control participants (HCs) scanned twice, 2.84 ± 1.63 years apart on average. We estimated subcortical volumes using FreeSurfer longitudinal image processing stream and used linear mixed models to assess the bidirectional relationship between baseline body mass index (BMI) or BMI change and hippocampal volume or volume change. While the hippocampus was our a priori region of interest, we repeated these analyses in other subcortical regions.

RESULTS: Baseline BMI predicted future hippocampal atrophy, but baseline brain structure did not predict future weight changes. BMI increased significantly over time ($F_{1,1085} = 15.98$, $p < .001$). Individuals with lower baseline BMI experienced greater weight gain ($F_{1,922} = 105.12$, $p < .001$). Greater weight gain was associated with greater hippocampal atrophy over time ($F_{1,899} = 16.33$, $p = .001$), more so in participants with BD than HCs ($F_{1,898} = 6.91$, $p = .009$). Consequently, lower baseline BMI predicted greater future hippocampal volume loss ($F_{1,904} = 14.77$, $p < .001$). These associations were not observed in other subcortical regions.

CONCLUSIONS: Our findings suggest that weight gain is a modifiable risk factor for hippocampal atrophy, especially in individuals with lower BMI and those with BD. Prevention of weight gain in general, but especially in people with BD, could provide neuroprotective benefits.

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Obesity is among the most expensive public health challenges, with its projected economic impact reaching 4.32 trillion dollars by 2035, comparable to the global expenditure of the COVID-19 pandemic (1). Since the 1990s, obesity rates worldwide have doubled among adults and quadrupled in adolescents (2). These rates are expected to continue rising in low- and middle-income countries and to double in high-income countries (3). Certain populations are especially

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vulnerable to obesity, such as individuals with bipolar disorder (BD), who are 3 to 5 times more likely to become obese relative to the general population (4). A recent large study confirmed that individuals with BD have higher average body mass index (BMI), higher rates of obesity, and steeper BMI increase over time compared with healthy control participants (HCs) (5). Regardless of the many reasons for the higher obesity rates in BD (e.g., medications, symptoms, genetic overlap, common risk factors), it remains key to study what the combined presence of BD and obesity means for the future development of relevant health outcomes.

The impact of obesity on medical health is generally well recognized. Obesity or obesity-related illnesses are among the leading contributors to both mortality and disability (6,7). However, it is much less acknowledged that the brain is one of the targets for obesity-related structural and functional changes long before the onset of macrovascular complications such as stroke. Midlife obesity is one of the strongest risk factors not only for vascular dementia but also for Alzheimer's disease (8–10). More specifically, obesity is linked to lower cortical thickness/subcortical volumes and worse cognitive functioning even when controlling for other cardiovascular risk factors (11–16). These effects of obesity on brain structure and function are worrisome in general, but especially in people with BD, where obesity may interact with brain alterations specific to the psychiatric disorder. Both obesity and BD are linked to brain changes in many of the same regions, including the hippocampus (15,17–22). Large-scale studies have shown that in these overlapping regions, obesity adds to the effects of BD, such that individuals with both conditions have more pronounced brain changes than those with one or none (23,24).

However, most of these findings come from cross-sectional studies, and while informative, they cannot determine the temporal direction of associations. It is possible that certain brain alterations may predispose individuals to obesity through heightened impulsivity (25,26), hypothalamic-pituitary-adrenal axis dysregulation (27), or reward signal disruption (28,29). Conversely, it is possible that weight or weight gain could contribute to subsequent brain changes through chronic low-grade inflammation (30), astrocyte activation (31), glutamatergic excitotoxicity (32), insulin resistance (33–35), mitochondrial dysfunction/oxidative stress (36,37), hypercortisolemia (38), microangiopathy (39), etc. While observational longitudinal studies cannot determine causality, they can inform us about temporality, i.e., what came first, whether brain alterations or obesity.

Prospective brain imaging studies, including the largest reported to date, have shown that BD is associated with changes in the brain longitudinally (40). However, it remains unclear whether, and to what extent, obesity contributes to brain atrophy in individuals with BD. A single study demonstrated that clinically significant weight gain was linked to volume loss in several brain regions and to lower structural integrity of the hippocampus in first-episode mania (41,42). However, no studies have tested both possible directions of the association, i.e., brain structure predicting future weight gain or weight predicting future brain changes.

In addition, prior studies of BD or obesity have typically explored associations across many brain regions of interest (ROIs). While exploratory analyses help identify patterns and develop new hypotheses, there is now enough evidence for a priori selection of ROIs. It is well known that certain brain regions are more susceptible to external or internal factors than others. The hippocampus is a particularly plastic region, which is highly sensitive to allostatic load (i.e., adaptations to various environmental challenges) (38,43–45). Smaller hippocampal volumes are associated with many neuropsychiatric disorders, including BD (21,22), as well as metabolic alterations, including obesity (15,17–20). Therefore, the hippocampus is an optimal a priori region for investigating the effects of BD and obesity.

Here, we attempted to address these methodological considerations and knowledge gaps. To better understand the temporal sequence of associations between obesity and brain changes, we performed a longitudinal study. Collaboration with the ENIGMA (Enhancing NeuroImaging Genetics through Meta Analysis) consortium allowed us to compile a large sample of almost a thousand participants recruited across 13 sites globally. This provided a generalizable snapshot of BD and increased our statistical power to test the independent and interactive effects of both BD and obesity. To facilitate interpretation, we chose the hippocampus as our a priori ROI. Our primary research question was whether baseline BMI or greater weight gain predicted greater hippocampal atrophy over time or whether baseline hippocampal volume predicted greater future weight changes.

METHODS AND MATERIALS

This project was conducted in partnership with the ENIGMA Bipolar Disorder and BMIx Working Groups (23,40,46,47). See Table S1 for detailed site info and Table S2 for site exclusion criteria. All sites obtained approval from their ethics review board before contributing data.

Data Collection

Brain Imaging. Three-dimensional volumetric T1-weighted anatomical brain images were acquired at each site (see Table S3 for acquisition parameters). Because the study was longitudinal, participants underwent baseline and follow-up investigation at each site using the same protocol and scanner. ENIGMA-standardized image processing, quality control, and data extraction tools were applied as in a previous longitudinal study from the consortium (40) (see methodological details in the Supplement). Briefly, FreeSurfer (48–51) was used at each site to perform subcortical segmentations at each imaging time point. Images were processed with the longitudinal image processing stream implemented in FreeSurfer (version 5.3 or higher) (52). We included volumetric measures of the following subcortical structures: the nucleus accumbens, amygdala, hippocampus, pallidum, putamen, caudate, thalamus, and lateral ventricles, along with mean cortical thickness.

Visual quality controls were performed on an ROI level aided by the ENIGMA-standardized visual inspection guide including pass/fail parcellation examples, all of which are publicly available (https://github.com/ENIGMA-git). Although imaging data was collected using different scanners, we controlled for site differences by including the random effect

of site in our statistical models, similar to other previous ENIGMA studies (24,47).

Covariates. In addition to neurostructural phenotypes, we also collected the ENIGMA wave 1 covariates including diagnosis (Dx); age; sex (female/male); current treatment with lithium (Li), antiepileptics, generation I antipsychotics, generation II antipsychotics, or antidepressants; age of onset of Dx; history of psychosis; scanning site (where participants were scanned); and participant mood state at the time of the scan (euthymic, depressed, manic). We also obtained BMI for all individuals as it is an easily accessible measure of obesity. We did not have the exact date on which BMI was measured at each individual site. While weight fluctuations within days add a small amount of random noise, the within-subjects design with years between the scans and the large sample size help alleviate this issue. Serum biomarkers or other measures of obesity were not consistently available across the sites and could not be used.

Statistical Analysis

Statistical analyses were completed using R (53). For linear regression models, we used linear mixed models (package *nlme*, version 3.1-162). All model specifications are outlined in the Supplement (R Model syntax). All models controlled for random effects of data collection site. Models with repeated measures also controlled for random effects of participant and hemisphere. Any changes were calculated as follow-up minus baseline (time 2 minus time 1).

We compared clinical and demographic measures in the groups (BD vs. HC) using independent samples *t* tests for continuous variables and χ^2 tests for categorical variables. In a within-subjects/repeated-measures multiple regression analyses, we compared BMI at baseline and follow-up while controlling for interval, Dx, age, and sex.

To test our specific hypotheses, we first determined whether baseline brain structure predicted future weight gain. To this end, we tested whether baseline hippocampal volumes interacted with interval to predict change in BMI (dependent variable), while adjusting for baseline BMI, Dx, age, and sex. Next, we tested whether baseline BMI predicted future brain changes. Specifically, we tested whether baseline BMI interacted with interval to predict future changes in hippocampal volume (dependent variable), while adjusting for baseline volume, Dx, age, sex, hemisphere, and total intracranial volume (ICV). This model first included a 3-way interaction between baseline BMI, interval, and Dx, which was removed if nonsignificant. As hippocampal volume changes were our a priori target, we reported nominal *p* values for this region. Even though we expected to find a positive association between baseline BMI and hippocampal atrophy, we used a 2-tailed threshold to remain conservative and because 1-tailed tests are generally discouraged. To study the specificity of obesity-related changes to the hippocampus, we subsequently repeated the analyses described above for the other 7 subcortical regions (nucleus accumbens, amygdala, pallidum, putamen, caudate, thalamus, and lateral ventricles) and for cortical thickness. For these exploratory analyses, we reported false discovery rate–adjusted *p* values to control for multiple comparisons across regions.

Analyses focusing on baseline measures as predictors of future outcomes are clinically relevant and mimic a clinical assessment focusing on prognostic markers. This also fits with our initial strategy to test whether baseline brain structure predicted future weight gain or whether baseline BMI predicted future brain change. The unique benefit of a longitudinal study is that it also allows us to study dynamic predictors, i.e., to investigate the association between BMI change and brain changes. This is complementary to using baseline measures and informs interpretation/provides more mechanistic explanation of any changes. Consequently, we tested whether 1) baseline BMI predicted change in BMI while adjusting for age, sex, Dx, and interval and 2) whether change in BMI or its interaction with Dx predicted change in hippocampal volume while adjusting for baseline BMI, baseline volume, interval, age, sex, and ICV. To gain a better understanding of the effects of baseline BMI, we also included a cross-sectional analysis of baseline hippocampal volume, predicted by baseline BMI and its interaction with Dx, while adjusting for age, sex, and ICV.

We considered potential confounding of our results by relevant clinical variables, including medications and mood state. Consistent with previous ENIGMA studies (23,24,46), we tested the association between the number of jointly used medication classes (0–3 including antipsychotics [first or second generation], anticonvulsants, and antidepressants) and baseline BMI (adjusting for age and sex), change in BMI (adjusting for age, sex, baseline BMI, and interval), or change in subcortical volume (adjusting for age, sex, baseline BMI, change in BMI, baseline volume, ICV, and interval). In the same models, we separately estimated the effects of current Li treatment. The decision to analyze Li separately was motivated by Li's predominantly showing a positive association with subcortical volumes (22,54), whereas antipsychotics and anticonvulsants are predominantly negatively associated (24,55–57). In separate analyses, we also tested the associations between specific medications treated as separate predictors in the same model, with baseline BMI, change in BMI, or subcortical volume.

Lastly, we tested whether BMI change was predicted by mood state while adjusting for age, sex, interval, and baseline BMI. We also tested whether hippocampal volume change was predicted by mood state while adjusting for age, sex, baseline hippocampal volume, ICV, and interval.

RESULTS

Sample

We included 934 participants (233 with BD) from 13 data collection sites. The two visits for each participant were 2.84 years apart on average (SD = 1.63). Participants with BD were significantly younger, with higher BMI and greater rates of obesity (see Table 1 and Table S1). Between baseline and follow-up, BMI increased by 0.22 points per year (SD = 1.15; $F_{1,1085} = 15.98$, $p < .001$), while the rate of change did not differ between the groups ($F_{1,934} = 0.18$, $p = .669$).

What Comes First: Brain Changes or Obesity?

While baseline hippocampal volume did not predict future BMI change ($F_{1,898} = 0.12$, $p = .727$), baseline BMI did predict

Table 1. Sample Description: Demographic and Clinical Characteristics of Participant Groups at Baseline

	BD, n = 233	Control, n = 701	Group Difference
Age, Years	37.26 (14.00)	42.12 (17.52)	$t_{932} = 3.85$, $p < .001$
Sex, Female	100 (42.9%)	284 (40.5%)	$\chi^2_1 = 0.32$, $p = .569$
Interval, Years	3.72 (2.08)	2.55 (1.33)	$t_{932} = 9.96$, $p < .001$
Baseline BMI	26.47 (5.71)	24.40 (4.17)	$t_{932} = 5.94$, $p < .001$
Annual BMI Change	0.24 (1.25)	0.22 (1.13)	–
Baseline BMI Categories			
Normal	117 (50.2%)	436 (62.2%)	$\chi^2_2 = 26.49$, $p < .001$
Overweight	71 (30.5%)	211 (30.1%)	
Obese	45 (19.3%)	54 (7.7%)	
Age of Onset, Years	22.73 (10.07)	–	–
Diagnosis, BD-II	79 (33.9%)	–	–
Mood State			
Depressed	48 (21.4%)	–	–
Euthymic	157 (70.1%)	–	–
Manic	15 (6.7%)	–	–
Mixed	4 (1.8%)	–	–
Medications			
Antidepressant	75 (32.3%)	–	–
Anticonvulsant	85 (36.6%)	–	–
Antipsychotic, G1	19 (8.2%)	–	–
Antipsychotic, G2	95 (51.9%)	–	–
Lithium	83 (36.1%)	–	–

Values are presented as mean (SD) or n (%). Medication information reflects treatment at baseline.

BD, bipolar disorder; BMI, body mass index; G1, first generation; G2, second generation.

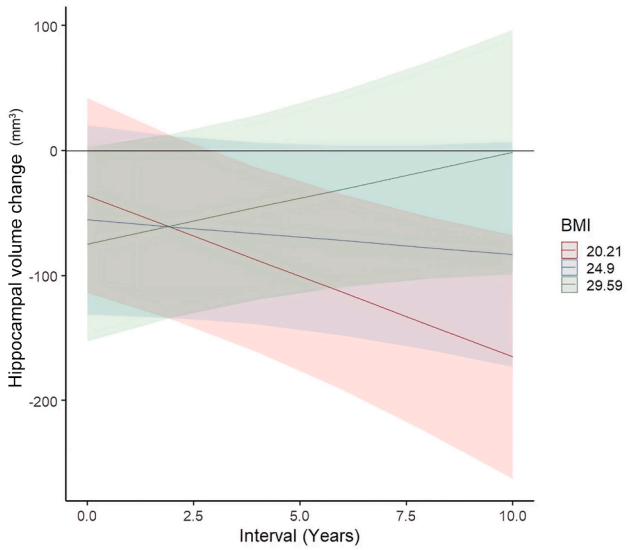


Figure 1. Change in hippocampal volume predicted by an interaction between baseline body mass index (BMI) and interval between the scans. Lower baseline BMI predicts greater hippocampal atrophy (in mm^3) over time than higher baseline BMI. While in the statistical model, BMI was treated as a continuous variable, to provide a clearer visualization, we divided baseline BMI into quantiles. The numbers (20.21, 24.9, 29.59) represent the 25%, 50%, and 75% percentiles of the BMI distributions in our study population, respectively. Confidence intervals for each are depicted in respective colors.

future hippocampal volume decrease (atrophy). Specifically, those with lower baseline BMI demonstrated greater hippocampal loss at longer intervals ($F_{1,904} = 14.77$, $p < .001$) (see Figure 1). There was no Dx × BMI × interval interaction ($F_{1,904} = 1.58$, $p = .210$) and no main effect of BD ($F_{1,904} = 0.42$, $p = .518$).

Weight Gain–Related Changes

Lower baseline BMI predicted greater BMI increase between the two scans in both groups ($F_{1,922} = 105.12$, $p < .001$) (Figure 2A). In a model containing both baseline BMI and BMI change, only greater BMI increase predicted greater hippocampal atrophy over time ($F_{1,899} = 16.33$, $p = .001$), and this effect was more pronounced in participants with BD ($F_{1,898} = 6.91$, $p = .009$) (Figure 2B).

Baseline BMI Versus Baseline Hippocampal Volume

In the cross-sectional analysis, there was a significant association between higher baseline BMI and smaller baseline hippocampal volume, which was more pronounced in individuals with BD than in HCs ($F_{1,917} = 3.97$, $p = .047$).

Exploratory Analyses

Baseline volume of any subcortical region or cortical thickness did not predict future change in BMI (see Table 2). Similarly, baseline BMI did not predict future changes in any other subcortical regions or in overall cortical thickness (see Table 3).

Influence of Clinical Variables

Most participants with BD were treated with polypharmacy (85%). Number of medication classes (0–3, including antipsychotics, anticonvulsants, and antidepressants) was associated with higher baseline BMI ($F_{1,221} = 3.94$, $p = .048$), and higher BMI increase between scans ($F_{1,211} = 12.30$, $p < .001$), but was not significantly associated with any subcortical volume changes for any region. Treatment with Li was not significantly associated with baseline BMI ($F_{2,221} = 0.05$, $p = .819$), change in BMI ($F_{2,220} = 0.14$, $p = .713$), or hippocampal atrophy ($F_{1,205} = 2.01$, $p = .157$).

When we modeled each medication class as a separate predictor, none were significantly associated with baseline BMI. Antidepressant use was associated with greater BMI increase over time (see Table S4). However, antipsychotic ($F_{1,203} = 0.70$, $p = .405$), anticonvulsant ($F_{1,203} = 0.32$, $p = .569$), antidepressant ($F_{1,203} = 0.52$, $p = .471$), and Li ($F_{1,203} = 2.23$, $p = .138$) use were not significant predictors of hippocampal atrophy.

Mood state did not predict change in BMI ($F_{1,198} = 0.86$, $p = .463$) or hippocampal atrophy ($F_{1,197} = 1.03$, $p = .381$).

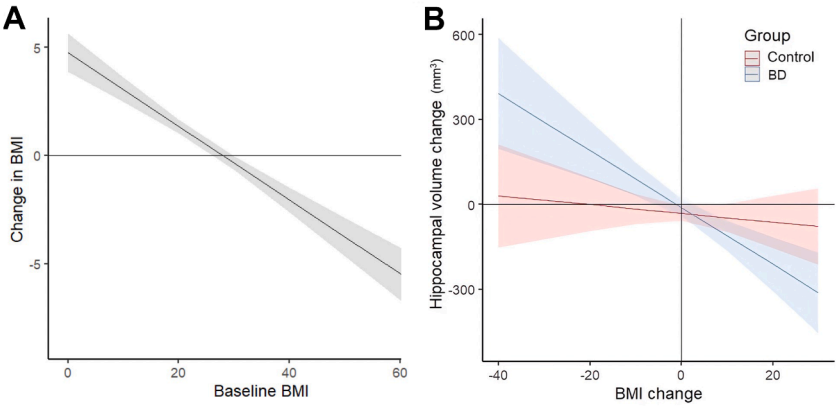


Figure 2. Associations with body mass index (BMI) change. **(A)** Association between BMI and BMI change. Lower baseline BMI was associated with greater weight gain, while adjusting for age, sex, and diagnosis. **(B)** Weight gain–related hippocampal atrophy stratified by diagnosis. The association between BMI increase and hippocampal atrophy was significantly more pronounced in participants with bipolar disorder (BD) than in control participants.

DISCUSSION

Baseline BMI predicted future hippocampal atrophy, while baseline brain structure did not predict future change in weight. More specifically, lower baseline BMI predicted greater future decrease in hippocampal volume. This initially surprising effect of baseline BMI was explained by weight gain, as lower baseline BMI was associated with future weight gain, and weight gain between the scans was a stronger predictor of hippocampal atrophy than baseline BMI. While the association between BMI increase and hippocampal volume decrease was evident in both groups, it was more pronounced in individuals with BD than in HCs. Taken together, these findings demonstrate that weight gain was a risk factor for hippocampal atrophy, especially in individuals with low to normal BMI and those with BD.

Even though a longitudinal study does not prove causality, it does demonstrate temporality. Here, we showed an association between baseline BMI and future brain changes but not between baseline brain structure and future weight gain. This is consistent with Mendelian randomization studies that suggest that obesity causes brain alterations rather than the opposite (i.e., brain changes lead to obesity) (58–60). The direction from obesity to brain changes is further supported by weight loss studies, which suggest reversibility. Our results mirror the replicated evidence of associations between weight loss following bariatric surgery and increases in hippocampal volumes (61,62). While these studies focused on extreme obesity (average BMI of 41.4 across the studies) and substantial weight fluctuations (with a BMI reduction of up to 14.9), we were still able to detect hippocampal volume changes in a sample with an average yearly BMI increase of 0.22 points. Taken together, these results suggest a causal effect of weight gain on brain changes.

While the finding that lower baseline BMI predicted greater hippocampal atrophy initially seemed surprising, the association between low baseline BMI and greater weight gain mechanistically explained it. In a model containing both baseline BMI as well as BMI change, only BMI change was associated with hippocampal atrophy. Thus, the effect of baseline BMI on hippocampal atrophy was primarily driven by longitudinal weight change, with no additional contribution of the baseline BMI. Furthermore, in cross-sectional analyses, higher baseline BMI predicted lower baseline hippocampal volume. This further supports our conclusion that low baseline BMI is simply a proxy for weight gain and not damaging in itself. Taken together, these results strengthen our conclusions that weight gain, rather than baseline weight, was the critical factor here.

Table 2. Baseline Brain Structure Predicting Future BMI Changes

Region	Estimate (SE)	Significance, p_{FDR}
Lateral Ventricles	5.1×10^{-6} (9.7×10^{-6})	$F_{1,908} = 0.27$, $p = .690$
Thalamus	2.9×10^{-5} (4.3×10^{-5})	$F_{1,841} = 0.46$, $p = .690$
Caudate	1.6×10^{-5} (8.5×10^{-5})	$F_{1,903} = 3.74$, $p = .141$
Putamen	1.1×10^{-5} (5.4×10^{-5})	$F_{1,884} = 4.21$, $p = .141$
Pallidum	2.8×10^{-5} (1.5×10^{-4})	$F_{1,882} = 3.14$, $p = .154$
Hippocampus	3.3×10^{-5} (9.6×10^{-5})	$F_{1,898} = 0.12$, $p = .727$
Amygdala	1.1×10^{-4} (2.0×10^{-4})	$F_{1,900} = 0.28$, $p = .690$
Cortical Thickness	9.0 (0.45)	$F_{1,905} = 3.99$, $p = .141$

Interaction between baseline regions of interest and interval in predicting changes in BMI, while adjusting for age, sex, diagnosis, and baseline BMI.

BMI, body mass index; FDR, false discovery rate.

Table 3. Baseline BMI Predicting Future Brain Changes

Region	Estimate (SE)	Significance, p_{FDR}
Lateral Ventricles	−5.93 (4.29)	$F_{1,914} = 1.90$, $p = .369$
Thalamus	1.07 (1.16)	$F_{1,842} = 0.85$, $p = .477$
Caudate	0.84 (0.68)	$F_{1,909} = 1.52$, $p = .369$
Putamen	1.27 (0.88)	$F_{1,890} = 2.10$, $p = .369$
Pallidum	0.03 (0.34)	$F_{1,888} = 0.01$, $p = .933$
Hippocampus	2.16 (0.56)	$F_{1,904} = 14.77$, $p = .001$[a]
Amygdala	−0.29 (0.36)	$F_{1,906} = 0.64$, $p = .484$
Cortical Thickness	0.00028 (0.00023)	$F_{1,911} = 1.47$, $p = .369$

Interaction between baseline BMI and interval in predicting changes in ROI volume, while adjusting for age, sex, diagnosis, baseline ROI volume, and total ICV. See Figure 1 for visualization of the hippocampal results.

BMI, body mass index; FDR, false discovery rate; ICV, intracranial volume; ROI, region of interest.

[a]The hippocampal volume changes were significant even after correction for multiple comparisons.

A single previous longitudinal study in the general population in individuals with higher average baseline age (63 years) and higher average baseline BMI (26.51) but minimal change in BMI over time found that higher baseline BMI was associated with lower baseline hippocampal volume and greater hippocampal atrophy (an additional 0.2% hippocampal atrophy per unit of BMI) over the 8-year follow-up (63). In a younger population, such as in our study, many individuals gain weight but have not been exposed to the long-term effects of obesity. In contrast, older participants may no longer gain that much weight but have likely been exposed to obesity and a growing number of obesity-related comorbidities for extended periods of time. Therefore, we would expect to see a greater effect of weight gain in a younger population and a greater effect of obesity in an older population. Regardless of these differences, the results converge on negative associations between either weight or weight gain and hippocampal volume.

Our results are consistent with prior cross-sectional studies of a negative association between higher weight and smaller hippocampal volumes in the general population (15,19,20,63). Similar to our findings, Bond *et al.* (64) found an association between BMI and lower hippocampal integrity (as measured by *N*-acetylaspartate [NAA]) in BD. Previous longitudinal studies also converge with our results. Specifically, clinically significant weight gain was associated with atrophy in the temporal lobes (middle temporal gyrus), which was more pronounced in participants with BD than in HCs (41) and with lower hippocampal NAA in both participants with BD and HCs (42). More broadly, another study also demonstrated an association between weight gain and hippocampal atrophy in people with first-episode psychosis (65).

We can only speculate about the mechanism underlying the potential effects of obesity on the brain. These include chronic low-grade inflammation (30), astrocyte activation (31), glutamatergic excitotoxicity (32), insulin resistance (33–35), mitochondrial damage/oxidative stress (36,37), hypercortisolemia (38), and microangiopathy (39). In people with BD, these mechanisms may be amplified by additional BD-related factors, such as episodes of illness that may impact the brain via similar mechanisms (66). This could explain why the effect of BMI change was more pronounced in individuals with BD than in HCs. Many of these mechanisms may be particularly damaging to the hippocampus, which has some of the highest levels of glucocorticoid receptors in the brain, is highly vascularized, and has a very high metabolic demand relative to other brain regions (38,43–45). These characteristics could underlie the greater sensitivity of hippocampus to the effects of weight gain.

Lower baseline BMI as a risk factor for future weight gain–related hippocampal atrophy has significant clinical implications. Our results emphasize prevention of weight gain, especially in people with BD, who showed a stronger association between BMI increase and hippocampal atrophy. Low to normal baseline BMI is also a risk factor for medication-related weight gain (67,68). Unlike other such risk factors, baseline BMI can be measured even before medications are started. Therefore, limiting prescriptions of obesogenic medications and emphasizing the use of more weight-neutral options (69) in people with low to normal BMI could help postpone or reduce weight gain, which in turn could also help preserve brain structure. Li, which may be neuroprotective (70) and has lower propensity for weight gain than antipsychotics (71), may be preferred when appropriate. If prevention is not possible, clinicians could consider pharmacological treatments such as metformin or novel GLP-1 agonists, which have unprecedented efficacy in managing weight. These results may also have implications for understanding and managing memory impairments, which are common in BD and closely linked to hippocampal atrophy.

The current study has important research implications. Given our findings and the increasing rates of obesity, it is critical in future studies of hippocampal volumes to control for BMI or weight gain, especially if the focus is on individuals with severe mental illness (SMI). Furthermore, the commonalities across SMIs in brain imaging findings, including hippocampal atrophy, which have puzzled researchers, could be explained by the shared presence of obesity across many psychiatric conditions. Through studying the mechanisms of brain changes related to weight gain, we could also gain insights into processes underpinning neuroprogression (72).

Our study has the following limitations. Anthropometric/metabolic markers, lifestyle factors, more detailed clinical information, and cognitive measures are not widely available from the ENIGMA collaborating sites, so we were unable to include those in our analyses. Our results did not appear confounded by medication use because most of our sample comprised HCs, and among participants with BD, there was no association between medication and hippocampal volume change. At the same time, the sensitivity to detect effects of medications on the brain might have been reduced by the fact that details about dosage, duration, and compliance were not available. It may not be obesity/weight gain that causes these changes but rather some metabolic alterations or other factors that are closely linked to obesity/weight gain, such as diet, sleep quality, or patterns of physical inactivity. Even if this were the case, obesity is still much easier to measure and thus more clinically applicable.

Our study has several strengths including the focus on a highly prevalent factor that has been ignored in most previous literature—the relatively large sample (nearly a thousand participants), which is uncommon in neuroimaging studies, especially longitudinal studies. The longitudinal design allowed us to understand the temporal directionality and to study both static and dynamic predictors, i.e. baseline BMI and BMI change. Study participants were recruited at 13 sites globally and thus are generalizable and represent a broad snapshot of BD around the globe, including people of different ancestries, cultural habits, and other factors. Aside from providing new results, we replicated many previously reported associations.

Conclusions

Our findings suggest that while brain structure did not predict future weight changes, baseline BMI and weight gain did predict future hippocampal atrophy. Specifically, hippocampal atrophy was most closely linked to weight gain, which was most likely in people with lower baseline BMI. Maintaining healthy weight and preventing weight gain may protect the

hippocampus, especially in people with BD. Future studies should link these longitudinal changes in the hippocampus to future changes in cognition and should study the impact of weight loss medications such as GLP-1 agonists on the brain and cognitive functioning.

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REFERENCES

1. World Health Organization: Obesity. Available at: https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity. Accessed June 9, 2021.
2. World Health Organization: Dementia. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia#:~:text=Dementia%20is%20currently%20the%20seventh,dependency%20among%20older%20people%20globally. Accessed March 1, 2023.
3. Koliaki C, Dalamaga M, Liatis S (2023): Update on the obesity epidemic: After the sudden rise, is the upward trajectory beginning to flatten? Curr Obes Rep 12:514–527.
4. Afzal M, Siddiqi N, Ahmad B, Afsheen N, Aslam F, Ali A, *et al.* (2021): Prevalence of overweight and obesity in people with severe mental illness: Systematic review and meta-analysis. Front Endocrinol 12:769309.
5. Najar H, Joas E, Jonsson V, Pålsson E, Landén M (2024): Recent secular trends of body mass index in individuals with bipolar disorders and in the general population. Am J Psychiatry 181:39–46.
6. Abdelaal M, le Roux CW, Docherty NG (2017): Morbidity and mortality associated with obesity. Ann Transl Med 5:161.
7. Word Health Organization. In: Kluge HHP editor. WHO European Regional Obesity Report 2022, (2022). Copenhagen: World Health Organization.
8. Beydoun MA, Beydoun HA, Wang Y (2008): Obesity and central obesity as risk factors for incident dementia and its subtypes: A systematic review and meta-analysis. Obes Rev 9:204–218.
9. Stephan BCM, Cochrane L, Kafadar AH, Brain J, Burton E, Myers B, *et al.* (2024): Population attributable fractions of modifiable risk factors for dementia: A systematic review and meta-analysis. Lancet Healthy Longev 5:e406–e421.
10. Qu Y, Hu HY, Ou YN, Shen XN, Xu W, Wang ZT, *et al.* (2020): Association of body mass index with risk of cognitive impairment and dementia: A systematic review and meta-analysis of prospective studies. Neurosci Biobehav Rev 115:189–198.
11. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB (2003): Lower cognitive function in the presence of obesity and hypertension: The Framingham Heart Study. Int J Obes Relat Metab Disord 27:260–268.
12. Yang Y, Shields GS, Guo C, Liu Y (2018): Executive function performance in obesity and overweight individuals: A meta-analysis and review. Neurosci Biobehav Rev 84:225–244.
13. Maksyutynska K, Stogios N, Prasad F, Gill J, Hamza Z, De R, *et al.* (2024): Neurocognitive correlates of metabolic dysregulation in individuals with mood disorders: A systematic review and meta-analysis. Psychol Med 54:1245–1271.
14. Dekkers IA, Jansen PR, Lamb HJ (2019): Obesity, brain volume, and white matter microstructure at MRI: A cross-sectional UK Biobank study. Radiology 291:763–771.
15. Janowitz D, Wittfeld K, Terock J, Freyberger HJ, Hegenscheid K, Völzke H, *et al.* (2015): Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. Neuroimage 122:149–157.
16. Opel N, Thalamuthu A, Milaneschi Y, Grotegerd D, Flint C, Leenings R, *et al.* (2021): Brain structural abnormalities in obesity: Relation to age, genetic risk, and common psychiatric disorders: Evidence through univariate and multivariate mega-analysis including 6420 participants from the ENIGMA MDD working group. Mol Psychiatry 26:4839–4852.
17. Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, *et al.* (2010): Brain structure and obesity. Hum Brain Mapp 31:353–364.
18. Cherbuin N, Sargent-Cox K, Fraser M, Sachdev P, Anstey KJ (2015): Being overweight is associated with hippocampal atrophy: The PATH through Life Study. Int J Obes 39:1509–1514.
19. Suzuki H, Venkataraman AV, Bai W, Guitton F, Guo Y, Dehghan A, *et al.* (2019): Associations of regional brain structural differences with aging, modifiable risk factors for dementia, and cognitive performance. JAMA Netw Open 2:e1917257.
20. Ambikairajah A, Tabatabaei-Jafari H, Walsh E, Hornberger M, Cherbuin N (2020): Longitudinal changes in fat mass and the hippocampus. Obesity (Silver Spring) 28:1263–1269.
21. Haukvik UK, Gurholt TP, Nerland S, Elvsåshagen T, Akudjedu TN, Alda M, *et al.* (2022): In vivo hippocampal subfield volumes in bipolar disorder-A mega-analysis from the Enhancing Neuro Imaging Genetics Through Meta-Analysis Bipolar Disorder Working Group. Hum Brain Mapp 43:385–398.
22. Hajek T, Kopecek M, Höschl C, Alda M (2012): Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: A meta-analysis. J Psychiatry Neurosci 37:333–343.
23. McWhinney SR, Abé C, Alda M, Benedetti F, Bøen E, Del Mar Bonnin C, *et al.* (2023): Mega-analysis of association between obesity and cortical morphology in bipolar disorders: ENIGMA study in 2832 participants. Psychol Med 53:6743–6753.
24. McWhinney SR, Abé C, Alda M, Benedetti F, Bøen E, Del Mar Bonnin C, *et al.* (2021): Association between body mass index and subcortical brain volumes in bipolar disorders–ENIGMA study in 2735 individuals. Mol Psychiatry 26:6806–6819.
25. Bjorlie K, Fazzino TL (2020): Impulsivity as a risk factor for weight gain and body roundness change among college freshmen. Eat Behav 39:101435.
26. Bénard M, Camilleri GM, Etilé F, Méjean C, Bellisle F, Reach G, *et al.* (2017): Association between impulsivity and weight status in a general population. Nutrients 9:217.
27. Incollingo Rodriguez AC, Epel ES, White ML, Standen EC, Seckl JR, Tomiyama AJ (2015): Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: A systematic review. Psychoneuroendocrinology 62:301–318.
28. Kenny PJ (2011): Reward mechanisms in obesity: New insights and future directions. Neuron 69:664–679.
29. Verdejo-Román J, Vilar-López R, Navas JF, Soriano-Mas C, Verdejo-García A (2017): Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. Hum Brain Mapp 38:666–677.
30. Rohm TV, Meier DT, Olefsky JM, Donath MY (2022): Inflammation in obesity, diabetes, and related disorders. Immunity 55:31–55.
31. Obara-Michlewska M (2022): The contribution of astrocytes to obesity-associated metabolic disturbances. J Biomed Res 36:299–311.
32. Lloret A, Monllor P, Esteve D, Cervera-Ferri A, Lloret MA (2019): Obesity as a risk factor for Alzheimer's disease: Implication of leptin and glutamate. Front Neurosci 13:508.
33. Willette AA, Xu G, Johnson SC, Birdsill AC, Jonaitis EM, Sager MA, *et al.* (2012): Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. Diabetes Care 36:443–449.

34. Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M (2014): Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. Neuropsychopharmacology 39:2910–2918.
35. Hajek T, McIntyre R, Alda M (2016): Bipolar disorders, type 2 diabetes mellitus, and the brain. Curr Opin Psychiatry 29:1–6.
36. Morrison CD, Pistell PJ, Ingram DK, Johnson WD, Liu Y, Fernandez-Kim SO, *et al.* (2010): High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: Implications for decreased Nrf2 signaling. J Neurochem 114:1581–1589.
37. Woo CY, Jang JE, Lee SE, Koh EH, Lee KU (2019): Mitochondrial dysfunction in adipocytes as a primary cause of adipose tissue inflammation. Diabetes Metab J 43:247–256.
38. Sapolsky RM (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 57:925–935.
39. Purroy F, Sánchez E, Lecube A, Arqué G, Vicente-Pascual M, Mauri-Capdevila G, *et al.* (2021): Prevalence and predictors of cerebral microangiopathy determined by pulsatility index in an asymptomatic population from the ILERVAS project. Front Neurol 12:785640.
40. Abé C, Ching CRK, Liberg B, Lebedev AV, Agartz I, Akudjedu TN, *et al.* (2022): Longitudinal structural brain changes in bipolar disorder: A multicenter neuroimaging study of 1232 individuals by the ENIGMA Bipolar Disorder Working Group. Biol Psychiatry 91:582–592.
41. Bond DJ, Su W, Honer WG, Dhanoa T, Batres-Y-Carr T, Lee SS, *et al.* (2019): Weight gain as a predictor of frontal and temporal lobe volume loss in bipolar disorder: A prospective MRI study. Bipolar Disord 21:50–60.
42. Bond DJ, Silveira LE, Torres IJ, Lam RW, Yatham LN (2022): Weight gain as a risk factor for progressive neurochemical abnormalities in first episode mania patients: A longitudinal magnetic resonance spectroscopy study. Psychol Med 52:3783–3791.
43. McEwen BS (2001): Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. Ann N Y Acad Sci 933:265–277.
44. Ho N, Sommers MS, Lucki I (2013): Effects of diabetes on hippocampal neurogenesis: Links to cognition and depression. Neurosci Biobehav Rev 37:1346–1362.
45. Bonds JA, Shetti A, Stephen TKL, Bonini MG, Minshall RD, Lazarov O (2020): Deficits in hippocampal neurogenesis in obesity-dependent and -independent type-2 diabetes mellitus mouse models. Sci Rep 10:16368.
46. McWhinney S, Kolenic M, Franke K, Fialova M, Knytl P, Matejka M, *et al.* (2021): Obesity as a risk factor for accelerated brain ageing in first-episode psychosis-A longitudinal study. Schizophr Bull 47:1772–1781.
47. McWhinney SR, Brosch K, Calhoun VD, Crespo-Facorro B, Crossley NA, Dannlowski U, *et al.* (2022): Obesity and brain structure in schizophrenia—ENIGMA study in 3021 individuals. Mol Psychiatry 27:3731–3737.
48. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.
49. Fischl B, Van Der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, *et al.* (2004): Automatically parcellating the human cerebral cortex. Cereb Cortex 14:11–22.
50. Fischl B, Dale AM (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97:11050–11055.
51. Fischl B, Salat DH, Van Der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM (2004): Sequence-independent segmentation of magnetic resonance images. Neuroimage 23(suppl 1):S69–S84.
52. Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012): Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61:1402–1418.
53. R Core Team: R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: https://www.r-project.org. Accessed June 25, 2025.
54. Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A, *et al.* (2014): Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med 44:507–517.
55. Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC (2013): Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: A prospective longitudinal MRI study. Am J Psychiatry 170:609–615.
56. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 37:1680–1691.
57. Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, *et al.* (2011): Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Arch Gen Psychiatry 68:853–861.
58. Mulugeta A, Lumsden A, Hyppönen E (2021): Unlocking the causal link of metabolically different adiposity subtypes with brain volumes and the risks of dementia and stroke: A Mendelian randomization study. Neurobiol Aging 102:161–169.
59. Chen L, Zhao S, Wang Y, Niu X, Zhang B, Li X, Peng D (2023): Genetic insights into obesity and brain: Combine Mendelian randomization study and gene expression analysis. Brain Sci 13:892.
60. Chen W, Feng J, Guo J, Dong S, Li R, Ngo JCK, *et al.* (2023): Obesity causally influencing brain cortical structure: A Mendelian randomization study. Cereb Cortex 33:9409–9416.
61. Tuulari JJ, Karlsson HK, Antikainen O, Hirvonen J, Pham T, Salminen P, *et al.* (2016): Bariatric surgery induces white and grey matter density recovery in the morbidly obese: A voxel-based morphometric study. Hum Brain Mapp 37:3745–3756.
62. Zhang Y, Ji G, Xu M, Cai W, Zhu Q, Qian L, *et al.* (2016): Recovery of brain structural abnormalities in morbidly obese patients after bariatric surgery. Int J Obes (Lond) 40:1558–1565.
63. Cherbuin N, Sargent-Cox K, Fraser M, Sachdev P, Anstey KJ (2015): Being overweight is associated with hippocampal atrophy: The PATH through Life Study. Int J Obes (Lond) 39:1509–1514.
64. Bond DJ, Silveira LE, MacMillan EL, Torres IJ, Lang DJ, Su W, *et al.* (2017): Diagnosis and body mass index effects on hippocampal volumes and neurochemistry in bipolar disorder. Transl Psychiatry 7: e1071. [cited Dec 2 2025].
65. Jørgensen KN, Nesvåg R, Nerland S, Mørch-Johnsen L, Westlye LT, Lange EH, *et al.* (2017): Brain volume change in first-episode psychosis: An effect of antipsychotic medication independent of BMI change. Acta Psychiatr Scand 135:117–126.
66. Berk M, Conus P, Kapczinski F, Andreazza AC, Yücel M, Wood SJ, *et al.* (2010): From neuroprogression to neuroprotection: Implications for clinical care. Med J Aust 193:S36–S40.
67. Vochoskova K, McWhinney SR, Fialova M, Kolenic M, Spaniel F, Svancer P, *et al.* (2023): Weight and metabolic changes in early psychosis-Association with daily quantification of medication exposure during the first hospitalization. Acta Psychiatr Scand 148:265–276.
68. Vochoskova K, McWhinney SR, Fialova M, Kolenic M, Spaniel F, Furstova P, *et al.* (2024): Trajectories of daily antipsychotic use and weight gain in people hospitalized for the first episode of psychosis. Eur Psychiatry 67:e59.
69. Greger J, Aladeen T, Lewandowski E, Wojcik R, Westphal E, Rainka M, Capote H (2021): Comparison of the metabolic characteristics of newer second generation antipsychotics: Brexpiprazole, lurasidone, asenapine, cariprazine, and iloperidone with olanzapine as a comparator. J Clin Psychopharmacol 41:5–12.
70. Hajek T, Weiner MW (2016): Neuroprotective effects of lithium in human brain? Food for thought. Curr Alzheimer Res 13:862–872.
71. Gomes-da-Costa S, Marx W, Corponi F, Anmella G, Murru A, Pons-Cabrera MT, *et al.* (2022): Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 134:104266.
72. Yatham LN, Schaffer A, Kessing LV, Miskowiak K, Kapczinski F, Vieta E, *et al.* (2024): Early intervention, relapse prevention, and neuroprogression in bipolar disorder: The evidence matters. Bipolar Disord 26:313–316.