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Increased odds of high body mass index in depression with self-reported antidepressant use

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To the editor:

The incidence of depression and obesity is on the rise, posing significant public health concerns. While the literature largely supports a positive correlation between depression and body mass index (BMI),[1 2] earlier studies have suggested an inverse relationship[3] or indicated a lack of association between depression and obesity.[4]

Monoaminergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are the first-line treatment options for major depression. Research strongly supports a correlation between antidepressant use and weight gain, particularly in the case of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[5 6] However, there is limited evidence regarding the association between antidepressant use and BMI, with existing studies primarily focused on how obesity influences treatment outcomes.

Several mechanisms, including antidepressant use, have been proposed to explain the relationship between mood disorders and obesity.[7] Previous research demonstrated that depressive symptoms and antidepressant use were independently associated with BMI in postmenopausal women.[8] However, there were no subset analyses comparing individuals with depression who were taking antidepressants with those with depression who were not. Findings from another study showed that women with depression who had never used antidepressants had reduced odds of having an obese BMI.[9] Moreover, the positive relationship between antidepressant use and an obese BMI only became significant when analyses were limited to those with a history of depression.[9]

A large, population-level analysis is warranted to clarify the associations between depression, antidepressant use and BMI. This study investigated the independent associations of depression and self-reported antidepressant use (yes/no, antidepressant class and duration of use) with BMI. In a secondary analysis, the relationship between antidepressant use and BMI was investigated in a subset of participants with depression.

METHODS

Study population

This study used data from the 2007–2018 National Health and Nutrition Examination Surveys (NHANES), a cross-sectional survey conducted by the National Center for Health Statistics, part of the Centers for Disease Control and Prevention (CDC). NHANES uses a highly stratified multistage probability sampling design to assess the health and nutrition status of non-institutionalised US civilians. Descriptions of the survey protocol and sampling procedures can be found on the CDC website (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#).

Male and non-pregnant female participants ≥20 years of age with a BMI ≥18.5 kg/m^2 were included in this study. Participants were required to complete the Depression Screener (DPQ) and Prescription Medications Questionnaire. Participants who reported using combinations of prescription psychotropic medications (ie, bupropion with naltrexone, fluoxetine with olanzapine, amitriptyline with perphenazine or amitriptyline with chlordiazepoxide) or more than one class of antidepressant were excluded from all analyses.

Exposure variables

Participants self-reported the frequency of their depressive symptoms over the past 2 weeks in response to items DPQ010 through DPQ090, the nine questions of the Patient

Health Questionnaire-9 (PHQ-9).[10] The PHQ-9 is a reliable and valid measure of depression, aligned with the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition.[10] Each symptom was scored on a 4-point scale ranging from 0 (not experienced) to 3 (experienced nearly every day). The responses to each of the items were summed, with a score ≥10 indicating the presence of depression.[10]

Participants were asked if they had taken prescription medications within the past 30 days. Those who answered 'yes' were asked to either present their medication containers or, if unavailable, verbally report the name of the medication. The full list of generic names of antidepressants that were permitted for inclusion in this study, along with their classes, is provided in online supplemental table 1. Participants using 'unspecified' antidepressants were categorised as 'yes' for antidepressant use but were not included in analyses subset by class. Two participants who were using MAOIs were not included in antidepressant class analyses but were categorised as 'yes' for antidepressant use. Binary variables were constructed for each antidepressant class, where 'yes' indicated use of the specific antidepressant class, and 'no' indicated no use of the specific antidepressant class or no use of any antidepressant. Additionally, participants were asked to report their duration of antidepressant use, which was treated as a continuous variable measured in months.

Outcome variable

The outcome of this study was BMI (kg/m^2). Weight and height were measured by trained personnel in the Mobile Examination Center (MEC) and were used to calculate BMI. Values were categorised into healthy (≥18.5–<25 kg/m^2), overweight (≥25–<30 kg/m^2) and obese (≥30 kg/m^2).

Statistical analyses

All statistical analyses were performed using R V.4.2.2 and the package 'survey' to account for MEC survey weights. Survey weights were divided by six to account for the merging of six survey cycles. Continuous variables were presented as weighted mean (standard deviation, SD), while categorical variables were presented as weighted per cent. A χ^2 test of independence was used to assess statistically significant (p<0.05) differences in categorical demographic characteristics across participants with and without depression, and a t-test was used to test for differences in continuous variables. Multivariable ordinal logistic regression was used to examine the relationship between BMI (healthy vs overweight or obese) and depression, antidepressant use (yes/no, antidepressant class and duration of use) or antidepressant use (yes/no) among those with depression along with covariates. Proportional odds assumptions were met for all models, which were run based on an available case analysis. P values were adjusted using Holm's method in the antidepressant class analysis to account for multiple comparisons.

Potential covariates (ie, age, sex, race, poverty–income ratio, education, cigarette smoking status, alcohol use and minutes of sedentary activity per day) were selected based on prior work.[9] Age was definitively included in the model.[9] Univariate feature selection was then used to determine which of the remaining potential covariates were to be included in the final model if p<0.10. Final covariates for all models included age (continuous), sex (male, female), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race (including multiracial)), education (≤high school, >high school), cigarette smoking status (not at all, some days or every day), alcohol use (never in lifetime or in past 12 months, at least once in past 12 months) and minutes of sedentary activity per day (continuous). In addition to selected covariates, inclusion of depression status, total PHQ-9 score or antidepressant use as a control was implemented when appropriate.

RESULTS

The study population included 27 990 individuals (figure 1), of whom 7.41% were categorised as having depression and 11.81% reported using antidepressants. The mean (SD) age of participants was 47.84 (16.91) years old (range=20–80), and 49.92% were female. Across antidepressant classes, participants were most commonly using SSRIs (60.34%) (table 1). The overall mean (SD) duration of antidepressant use was 64.42 (73.34) months.

The unadjusted odds ratios (ORs) for all associations are presented in online supplemental file 1 and in online supplemental table 2. Participants with depression had greater odds of being in a higher BMI category compared with those without depression (adjusted OR (aOR) including antidepressant use=1.37, 95% confidence interval (CI): 1.22 to 1.55; p<0.001).

Compared with participants who were not using antidepressants, those who were using antidepressants had greater odds of being in a higher BMI category (aOR including depression status and total PHQ-9 score=1.36, 95% CI: 1.22 to 1.52; p<0.001).

After adjustment for covariates including depression status and total PHQ-9 score, participants who reported using SSRIs had greater odds of being in a higher BMI category compared with those who were not (ie, participants using SNRIs, TCAs, atypical antidepressants or not using any antidepressants) (aOR=1.45, 95% CI: 1.27 to 1.64; p<0.001, p-adjusted<0.001). Similarly, those who reported using SNRIs had greater odds of being in a higher BMI category compared with those who were not (ie, participants using SSRIs, TCAs, atypical antidepressants or not using any antidepressants), though this was insignificant after p value adjustment (aOR=1.32, 95% CI: 1.02 to 1.69; p=0.032, p-adjusted=0.095).

For every 1-month increase in duration of antidepressant use, the odds of being in a higher or lower BMI category were not significantly different (aOR including

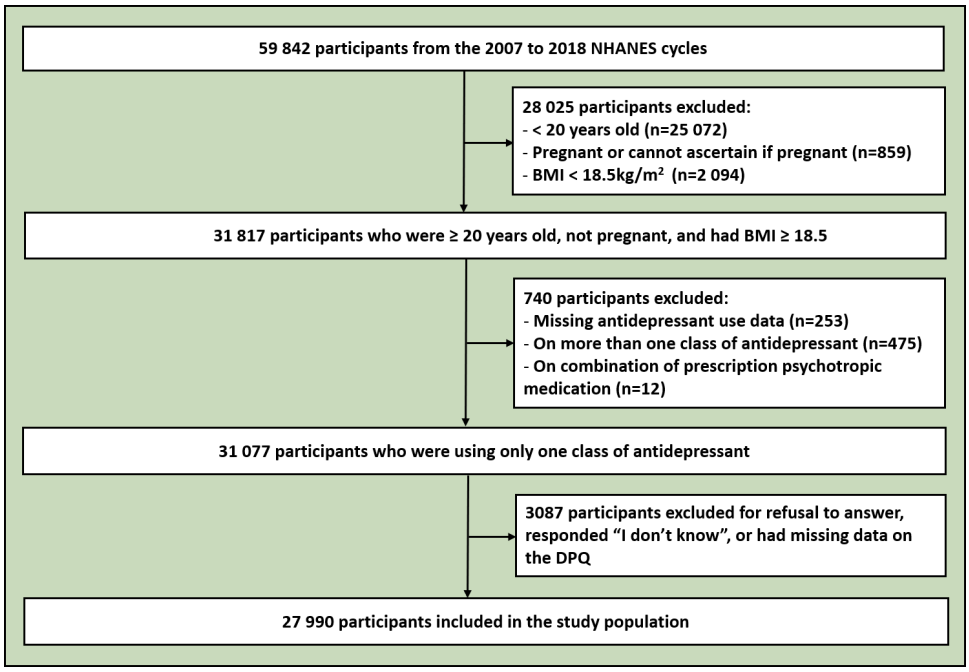

Figure 1 Participant inclusion flowchart. BMI, body mass index; DPQ, Mental Health-Depression Screener; NHANES, National Health and Nutrition Examination Survey.

depression status and total PHQ-9 score=1.00, 95% CI: 1.00 to 1.00; p=0.156).

Among participants with depression, those who were using antidepressants had greater odds of being in a higher BMI category compared with those who were not (aOR including total PHQ-9 score=1.61, 95% CI: 1.24 to 2.10; p<0.001).

DISCUSSION

This study investigated the independent associations of depression and self-reported antidepressant use with BMI, as well as the relationship between antidepressant use and BMI in a subset of participants with depression. Participants with depression had greater odds of being in a higher BMI category compared with those without depression. A similar trend was observed in participants who were using antidepressants compared with those who were not. Participants who were using SSRIs or SNRIs had increased odds of being in a higher BMI category compared with those who were not using antidepressants in each respective class, though the latter was statistically insignificant after p value adjustment. Among participants with depression, the odds of being in a higher BMI category were exacerbated in those who were using antidepressants compared with those who were not.

Our findings align with existing research demonstrating a positive association between depression and elevated BMI.[1 2] This correlation can be attributed to dietary changes and reduced physical activity typically observed in individuals with depression,[11] since increased depressive symptoms have been linked to lower odds of adhering to weight management and physical activity recommendations from healthcare providers.[12] Moreover, characteristics of depression, including physical symptoms, negative self-perceptions, depressed mood and lack of interest, have been robustly associated with obesity.[13] In contrast, individuals with a high BMI have higher amounts of adipocytes, which produce inflammatory markers such as interleukin 6 and C reactive protein. These markers can cause inflammation, a known factor involved in the pathophysiology of depression.[13 14] The presence of excess body fat, especially visceral fat, and underlying diseases caused by obesity can contribute to metabolic changes and depressive symptoms.[15] Although our study cannot establish causality and the relationship between depression and BMI may be bidirectional, it is noteworthy that one prior study suggested that obesity is related to an increased risk of future depression, whereas the opposite is not true.[16]

Our study reveals an association between antidepressant use and elevated BMI when controlling for depression. The potential contribution of monoamine pathways, encompassing serotonergic, adrenergic, histaminergic, cholinergic and dopaminergic receptors, might be one of the mechanisms underlying the observed association.[5] We found that participants who were using SSRIs and SNRIs had greater odds of having a high BMI compared with participants who were not using these antidepressants. While existing research regarding SSRI and SNRI antidepressants has yielded mixed findings as their effects might depend on the length of exposure,[5 6] SSRI and venlafaxine use have been associated with obesity risk.[17] We did not find a significant association between the duration of antidepressant use and BMI. This contrasts with previous research indicating that long-term treatment with citalopram, fluoxetine, mirtazapine and

Table 1 Demographic characteristics of the study population (n=27 990)

Characteristic	Depression—yes	Depression—no	Statistic	P value
Sample size	2405	25585		
Age*, mean (SD)	47.06 (16.05)	47.90 (16.97)	−1.68	0.097
Sex—female (%)	63.16	48.87	156.81	<0.001
Race (%)			53.08	<0.001
Mexican American	8.47	8.54		
Other Hispanic	8.62	5.59		
Non-Hispanic white	61.68	67.51		
Non-Hispanic black	13.51	10.79		
Other race—including multiracial	7.72	7.57		
Education—≤high school (%)	52.73	37.24	194.54	<0.001
Cigarette smoking—yes (%)	39.06	17.73	560.95	<0.001
Alcohol use—yes (%)	62.80	70.16	49.04	<0.001
Minutes sedentary activity/day*, mean (SD)	387.53 (222.58)	370.43 (200.88)	2.33	0.021
PHQ-9*, mean (SD)	13.94 (3.72)	2.08 (2.37)	133.76	<0.001
Antidepressant use—yes (%)†	32.02	10.20	877.00	<0.001
SSRI	58.32	60.87	12.26	0.477
SNRI	17.63	16.03	8.49	0.476
TCA	5.79	7.42	18.05	0.351
MAOI	0.00	0.19	10.92	0.501
Atypical	18.26	15.49	25.57	0.188
Unspecified	0.00	0.01	0.18	0.656
BMI (%)			104.64	<0.001
Normal	25.21	28.59		
Overweight	26.31	34.07		
Obese	48.48	37.34		

Categorical characteristics reported as weighted per cent; continuous characteristics reported as weighted mean (SD). χ^2 statistics values are given.
*Denotes t-test statistics values.
†Antidepressant class subsets presented as weighted percent of total antidepressant users.
BMI, body mass index; MAOI, monoamine oxidase inhibitor; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

sertraline was associated with increased BMI.[18] This could be attributed to the grouping of various antidepressants or recall bias, as participants might have misreported the duration of their antidepressant use. It should be noted that there are additional factors, such as the lifetime duration of antidepressant use, that were not captured in the NHANES data, which may have also influenced the observed outcomes.

Our results indicated that the combination of depression and antidepressant use may increase the odds of having a high BMI. Both depression and antidepressant use affect the serotonergic, dopaminergic, glutamatergic and monoaminergic systems, which can contribute to weight gain.[5 19] It is possible that the mechanisms of depression and antidepressant use synergistically raise the odds of having an elevated BMI; however, causality cannot be established based on the present investigation. It is also possible that individuals with a higher BMI may receive different treatment for depression compared with those with a healthier BMI. Previous research has suggested that individuals with a higher BMI had lower odds of receiving psychotherapy,[20] which could explain the association between antidepressant use and BMI in depression.

The cross-sectional design of our study restricts our findings to establishing correlations and precludes an understanding of causality. Moreover, as is common with cross-sectional studies using self-reported questionnaires, non-response bias is a potential limitation in our research. While self-reported antidepressant use was validated through the presentation of medication containers, the possibility of misclassification cannot be entirely discounted. This study also did not consider comorbidities, such as diabetes, sleep apnea or endocrine disorders, or the use of other medications, such as metformin, semaglutide or synthetic thyroid, which are associated with an increased incidence of depression and may contribute to BMI. Despite these limitations, the use of anthropometric data for the objective measurement of BMI strengthens the reliability of this investigation.

Our study found that participants with depression or those using antidepressants had increased odds of having a high BMI. This was exacerbated when investigating antidepressant use among participants with depression.

The results also suggest that antidepressant class, but not duration of antidepressant use, might be linked to BMI. As the precise mechanisms responsible for these associations are not fully understood, further investigation into this phenomenon is warranted. Future research should employ alternative measures of duration of antidepressant use and consider class and duration of antidepressant use together to further evaluate the association with BMI in depression.

Contributors VKT and VB conceptualised the study. The investigation was led by VKT who was also responsible for writing the original draft with SM. MW accessed the data and conducted the data analysis. HJ and WL supervised formal analysis. Manuscript writing was supervised by VB. All authors were involved in the interpretation, provided critical revisions to the manuscript for intellectual content and contributed to editing. All authors read and approved the final manuscript.

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Patient consent for publication Not required.

Ethics approval This study involves human participants. The survey protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (protocol numbers 2005-06, 2011-17, 2018-01). Informed consent was obtained from participants prior to data collection.

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