Obesity Comorbidity in Unipolar Major Depressive Disorder: Refining the Core Phenotype

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ABSTRACT

Objective: While a significant body of research has demonstrated high comorbidity rates between depression and obesity, the vast majority of this work has considered depression as a unitary diagnosis. Given that increased appetite and weight gain are highly characteristic of the "atypical" subtype of depression, while classic depression is characterized by decreased appetite and weight loss, it would be important to examine whether increased obesity risk is consistent across the major vegetative subtypes of depression or is limited to the atypical subtype.

Method: Using data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), we identified 5,092 US adults with past or current major depression based on *DSM-IV-TR* criteria and 1,500 gender-matched controls. Each depressed subject was designated as having classic, atypical, or undifferentiated depression based on core vegetative symptoms. Logistic regression models examined rates of current obesity (defined as a current body mass index [kg/m^2] > 30) across the 3 depressive subgroups and nondepressed controls, adjusting for demographic differences. To limit the possible effect of current depressive symptoms on observed obesity rates, secondary analyses were completed in individuals with past depression only.

Results: Subjects with atypical depression had markedly elevated obesity rates compared to population controls and to other depressed subjects, with corresponding pairwise odds ratios consistently greater than 2.0 ($P < .001$). In contrast, obesity rates were not significantly different in subjects with classic depression and nondepressed controls. These results were manifest in individuals with either current or past depression and were independent of gender and age.

Conclusions: While many individuals with classic depression will present with obesity due to the high prevalence of both disorders, only atypical depression is associated with an elevated risk of obesity relative to the population at large. Refining the target phenotype(s) for future work on depression and obesity might improve our understanding, prevention, and treatment of this complex clinical problem.

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Major depressive disorder (MDD) and obesity are among the most common and disabling disorders of humankind, each with enormous personal, familial, and societal costs.[1–4] Of further concern, depression and obesity are highly comorbid with one another, establishing a complex clinical phenotype associated with high morbidity and poor treatment response.[5–7] Clearly, improving our understanding of depression-obesity comorbidity is a high priority for psychiatry and medicine as a whole.

One major challenge in studying complex diseases such as depression and obesity is their clinical and biological heterogeneity. In depression for example, many patients present with the classic neurovegetative symptoms of appetite loss and insomnia, while others present with "atypical" symptoms of increased appetite and hypersomnia. Yet other patients present with neither or both of these symptom profiles. Several demographic, clinical, and etiologic factors distinguish classic and atypical subgroups.[8–12] Given this heterogeneity, and the fundamental importance of eating behavior in the onset and maintenance of obesity, it may be critical to consider illness subtypes when studying depression/obesity links. Of note, the vast majority of depression/obesity comorbidity studies have not implemented this approach, having considered depression as a single diagnostic entity.

If the target phenotype(s) for obesity-depression comorbidity can be refined, this would lead to more efficient and targeted sampling for research studies, and help in the development of novel prevention and treatment programs for specific subgroups of patients.[13] On the basis of this premise, the goal of the current study was to use a large population sample to investigate whether core vegetative subtypes of major depression—that is, classic melancholic and atypical depression—have similar or distinct links with obesity as defined by the World Health Organization body mass index (BMI [kg/m^2]) cutoff of 30. Given the key role of increased eating behavior for the onset and maintenance of obesity on the one hand, and for atypical depression on the other, we hypothesized a priori that atypical depression, but not melancholic depression, would be associated with an increased obesity risk relative to nondepressed population controls. We report here our findings based on the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

METHOD

Sample

The 2001–2002 NESARC is a representative sample survey of the United States sponsored by the National Institute on Alcohol Abuse and Alcoholism.[14,15] The target population was the civilian noninstitutionalized population, 18 years and older, residing in the United States and the District of Columbia, including Alaska and Hawaii. Personal Interviews were performed face to face with

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Clinical Points

- Depression co-occurring with obesity is a common clinical presentation associated with significant morbidity.
- The heterogeneity of both depression and obesity makes it difficult to establish mechanisms of disease in these patients.
- The atypical subtype of depression has a much closer relationship with obesity than classic melancholic depression and should be a priority focus for work in the area of depression and obesity comorbidity.

43,093 respondents, with fieldwork conducted by the US Census Bureau. The sampling frame response rate was 99%, the household response rate was 89% and the person response rate was 93%, yielding an overall survey response rate of 81%.

The specific sampling procedures and weighting of NESARC data are described in detail elsewhere.[15] When necessary, weighted data were adjusted to be representative of the US population based on the 2000 census. Psychiatric diagnoses were derived from the Alcohol Use Disorder and Associated Disabilities Interview Schedule-*DSM-IV-TR* version (AUDADIS-IV).[14] This structured diagnostic assessment was administered by trained interviewers and has demonstrated reliability and validity for detecting psychiatric disorders in the community.[14] The research protocol, including informed consent procedures, received full ethical review and approval from the US Census Bureau and the US Office of Management and Budget.

Depressive Subgroup Definition

From the sample of 43,093 adults in the NESARC database, we first identified all individuals age 18–65 years who met lifetime criteria for 1 or more MDD episodes. Given the current focus on unipolar MDD, all individuals meeting criteria for either a hypomanic or a manic episode lifetime were excluded at this step.

While the AUDADIS-IV covers the *DSM-IV* criteria for major depressive disorder, it does not assess the full *DSM-IV* criteria for either atypical or melancholic features per se. We thus defined vegetative subtypes using the same method as implemented in prior epidemiologic studies with this same limitation.[16–19] Classic depression was defined based on the combination of loss of appetite and either initial or late insomnia during major depressive episodes, while atypical depression was defined by the combination of increased appetite and hypersomnia during major depressive episodes. A third depressive subgroup termed "undifferentiated" or "neither" was defined as having MDD lifetime but not meeting criteria for either the classic or the atypical subgroups. To simplify the analyses, 266 individuals who met lifetime criteria for both classic and atypical episodes (5% of all depressed individuals) were excluded.

Validating the Subgroups

To maximize the validity and generalizability of the major depressive subgroups defined above, we next compared the classic and atypical groups on several demographic and clinical features that have strongly differentiated them in past research,[10,11,19,20] using simple Pearson χ^2 analyses. We specifically examined whether the atypical group, relative to the classic group, exhibited a greater preponderance of female cases, more early-onset depression (before age 18 years), more fatigue (yes/no), and more rejection sensitivity (yes/no). Conversely, we examined whether subjects with classic depression exhibited more late-onset depression (after age 40 years) and more psychomotor agitation (yes/no) relative to the atypical group. Rejection sensitivity was defined as a yes response to the question, "Do you often worry about being criticized or rejected in social situations," as assessed in the survey section entitled "Usual Feelings and Actions."

To establish a comparison group that would reflect nondepressed population obesity rates, a nondepressed control group was selected randomly from the overall NESARC sample by using the "select cases, random sample of cases" option available with SPSS-15 software (SPSS Inc, Chicago, Illinois). The number of individuals selected for this purpose was 1,500, with oversampling of females to match the higher rate of depression in this gender.

Obesity was defined based on the World Health Organization BMI cutoff of > 30. To limit the potential impact of outliers, we excluded individuals with a current BMI of less than 15 or greater than 60.

Statistical Analysis

Demographic variables were first compared across the 4 main study groups (ie, classic depression, atypical depression, depression meeting neither classic nor atypical criteria, and controls) by using Pearson χ^2 for categorical variables and analysis of variance for continuous variables (ie, age). Next, BMIs were compared across the 4 groups by using analysis of covariance (ANCOVA), controlling for the demographic differences found between the groups. Post hoc pairwise comparisons were done by using Tukey T test. Rates of obesity were next compared across the 4 study groups using stepwise logistic regression. The first step of the regression included the demographic covariates that differed significantly across the study groups, while the main study group variable was entered at step 2. Pending significant results, pairwise group comparisons of obesity rates were examined using adjusted odds ratios (ORs) with 95% confidence intervals (CIs), again controlling for the demographic differences identified above.

At both a clinical and a theoretical level, it would be important to know if depression/obesity links are limited to individuals with active/recent depression or whether they are also evident in individuals with past depression only: ie, independent of state depression. To examine this question in the current dataset, each depressed subject was designated as having recent/current depression (ie, within the last

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Table 1. Demographic Characteristics of Subjects by Diagnostic Group

Characteristic	Classic Depression (n = 2,259) n	%	Atypical Depression (n = 815) n	%	Undifferentiated Depression (n = 2,018) n	%	Nondepressed Controls (n = 1,500) n	%	Statistic	*df*	*P* Value
Sex											
Female	1,568	69.4	643	78.9	1,322	65.5	1,049	69.9	$\chi^2 = 49.24$	3	< .001
Male	691	30.6	172	21.1	696	34.5	451	30.1			
Marital status											
Married or common-law	1,009	44.7	385	47.2	1,000	49.6	860	57.3	$\chi^2 = 152.46$	6	< .001
Never married	460	20.4	239	29.3	522	25.9	354	23.6			
Widowed/separated/divorced	790	35.0	191	23.4	496	24.6	286	19.1			
Total family income/year											
< $25,000	752	33.3	249	30.6	586	29.0	445	29.7	$\chi^2 = 14.68$	6	< .001
$25,000–$50,000	474	21.0	159	19.5	422	20.9	296	19.7			
> $50,000	1,033	44.7	407	49.9	1,010	50.0	759	50.6			
Education											
Some high school or less	333	14.7	81	9.9	240	11.9	204	13.6	$\chi^2 = 48.53$	6	< .001
Completed high school	526	23.3	156	19.1	407	20.2	395	26.3			
Postsecondary or more	1,400	62.0	578	70.9	1,371	67.9	901	60.1			
Employment											
Employed/school/homemaker	1,783	80.5	671	83.3	1,658	83.6	1,291	87.3	$\chi^2 = 49.21$	6	< .001
Unemployed	311	14.0	98	12.2	228	11.5	100	6.8			
Retired	120	5.4	37	4.6	98	4.9	87	5.9			
Age, mean ± SD, y	42.0 ± 12.1		39.3 ± 12.6		41.3 ± 12.4		40.6 ± 12.8		$F = 10.01$[a]	3,6588	< .001

[a]Analysis of variance.

12 months) or past depression only (last depressed more than 12 months ago). The logistic regression described above was then run separately in these 2 subgroups. Each of the 1,500 control subjects was randomly assigned to 1 of these 2 subanalyses, with oversampling of controls for the past-depression analysis to match the proportion of depressed individuals with past versus recent/current depression only (1.66:1).

To determine whether depression-group differences in obesity rates varied across the 2 genders, we repeated the first stepwise logistic regression described above removing gender as a covariate at step 1. The independent variables at step 2 included gender, depression group, and the gender × depression group interaction. Similarly, to examine whether depression group differences in obesity rates varied across the lifespan, each subject was assigned to 1 of 3 age strata: ie, 18–34, 35–49, or 50–65 years of age. A third logistic regression was then performed by removing age as a covariate at step 1 and using the age-strata, depression-group, and age-strata × depression-group interaction as independent variables.

Given the large sample size and high statistical power to detect small effects, the significance level was set at $P \leq .01$ for the primary group comparisons. Pairwise adjusted ORs were done using 95% CIs.

RESULTS

Sample Definition

After we excluded the 266 individuals with both classic and atypical episodes lifetime, the final sample for the current study included 3,533 female and 1,559 male individuals with unipolar MDD and 1,049 female and 451 male controls. Among the depressed subjects, 2,259 (44.4%) were designated as classic, 815 (16.0%) as atypical, and 2,018 (39.6%) as neither. The proportion of depressive subtypes defined by neurovegetative symptoms was highly consistent with several large community studies comparing atypical and classic depression.[10,17,20,21]

Demographics by Subgroup

Table 1 summarizes the demographic characteristics of the 4 study groups. As shown, there were significant differences across the groups in the proportion of female versus male subjects, marital status, education, employment, and current age. These 5 variables were thus used as covariates in the subsequent analyses described below.

Comparison and Validation of the Classic and Atypical Subgroups

Further analysis confirmed that, in our study sample, relative to classic depression, atypical depression was associated with a preponderance of female cases (78.9% vs 69.4%; $\chi^2 = 26.7$; $P < .001$), more early onset depression (23.3% vs 15.0%; $\chi^2 = 29.0$; $P < .001$), more reported fatigue (yes/no) (92.9% vs 81.3%; $\chi^2 = 60.3$; $P < .001$), and more rejection sensitivity (25.3% vs 19.2%; $\chi^2 = 13.2$; $P < .001$). Also consistent with the literature, classic depression was associated with more late-onset depression (24.3% vs 17.9%; $\chi^2 = 13.8$; $P < .001$) and more psychomotor agitation (45.0% vs 24.0%; $\chi^2 = 100.9$; $P < .001$) than was atypical depression. These various results support the validity and generalizability of the depressive subgroups defined in the current study.

BMIs in the Four Study Groups

Table 2 summarizes the mean current BMIs for each of the 4 study groups. An ANCOVA controlling for sex, marital status, education, employment, and current age revealed

Table 2. Marginal Means (with 95% CIs) for Body Mass Index by Study Group[a]

Variable	Classic Depression (A) (B), (n = 2,214)	Atypical Depression (n = 806)	Undifferentiated Depression (A), (n = 1,984)	Nondepressed Controls (B), (n = 1,478)	*F* Value (for group comparison)	*df*	*P* Value
Body mass index (kg/m^2), mean (95% CI)	26.8 (26.5–27.1)	30.5 (30.1–30.9)	27.4 (27.2–27.7)	26.8 (26.5–27.1)	79.3	(3,6473)	< .001

[a]Values are based on analysis of covariance controlling for sex, marital status, education, employment, and age. Shared letters in column headings indicate groups that do *not* significantly differ in mean body mass index based on pairwise comparisons. Sample size presented here varies from total sample size because of missing covariate data for the analysis of covariance.

Table 3. Rates of Current Obesity by Diagnostic Group

	Obese With Classic Depression (n = 2,259)		Obese With Atypical Depression (n = 815)		Obese With Undifferentiated Depression (n = 2,018)		Obese, Nondepressed Controls (n = 1,500)				
Group	n	%	n	%	n	%	n	%	χ^{2a}	*df*	*P* Value
All subjects	588	26.0	371	45.5	574	28.4	375	25.0	135.39	3	< .001
Current depression	208	23.9	145	48.2	230	30.9	113	25.7	75.44	3	< .001
Past depression only	380	27.4	226	44.0	344	27.0	262	24.7	68.16	3	< .001

[a]χ^2 for step 2 of logistic regression predicting obesity rates by group. Step 1 included sex, marital status, education, employment, and age.

Table 4. Adjusted[a] Odds Ratios for Obesity Rates by Study Group

Group	Classic vs Controls	Atypical vs Controls, OR (95% CI)	Undifferentiated vs Controls, OR (95% CI)	Classic vs Undifferentiated, OR (95% CI)	Atypical vs Undifferentiated, OR (95% CI)	Classic vs Atypical, OR (95% CI)
All subjects	NS	2.61 (2.16–3.16)**	NS	0.85 (0.74–0.97)*	2.27 (1.90–2.71)**	0.38 (0.32–0.45)**
Current MDD	NS	3.22 (2.34–4.44)**	1.38 (1.07–1.79)*	0.67 (0.53–0.84)**	2.40 (1.79–3.22)**	0.29 (0.22–0.39)**
Past MDD	NS	2.38 (1.87–3.01)**	NS	NS	2.22 (1.78–2.77)**	0.44 (0.35–0.55)**

[a]Adjusted for age, gender, marital status, education, and employment.
*P < .05; **P < .001.
Abbreviations: MDD = major depressive disorder, NS = nonsignificant.

a highly significant difference in BMI across the 4 groups ($F_{3,6473} = 79.3$, $P < .001$). Post hoc pairwise group comparisons using Tukey T test indicated that the atypical depression group had a significantly higher mean BMI than did each of the other 3 groups. The mean BMI in the classic depression group was not significantly different than that of either the undifferentiated depressed or control groups. The undifferentiated depressed group had a significantly higher mean BMI than did the nondepressed control group.

Rates of Obesity in the Four Study Groups

Table 3 summarizes the rates of current obesity across the 4 study groups in all study subjects and in those stratified according to recent/current versus past depression only. Adjusted ORs were used for the corresponding pairwise group comparisons, which are summarized in Table 4.

As shown in Table 3, when all subjects were included, there was a highly significant difference in obesity rates across the 4 study groups ($\chi^2_3 = 135.39$, $P < .001$, after we controlled for covariates). Table 4 further indicates that the atypical depressed group had markedly higher rates of obesity than did each of the other groups, in each case at a significance level of $P < .001$. There was no significant difference in obesity rates between the classic depressed group and the nondepressed control group. The classic depressed group had a significantly lower obesity rate than did the undifferentiated (neither) group at $P < .05$.

Table 3 further indicates that a highly significant difference in obesity rates by study group was also evident when the sample was limited to either recent/current depression or past depression only (with respective controls). Table 4 shows that, in both of these subanalyses, the atypical depressed group continued to have markedly higher obesity rates than each of the other groups (at $P < .001$ in each case). It would thus appear that obesity in atypical MDD subjects is not simply attributable to ongoing major depression but that it is more of a trait for these individuals. However, recent/current depression did make a difference for some of the other pairwise comparisons. In subjects with recent/current but not past depression only, undifferentiated MDD subjects (ie, with neither atypical nor classic episodes lifetime) had higher rates of obesity than did controls (at $P < .05$) or classically depressed subjects (at $P < .001$). This finding suggests that the symptoms of recent (possibly current) depression do influence the relative rates of obesity across the depressed subgroups to an extent.

Interaction effects related to gender or age group. When the gender × depressive subgroup interaction was included at step 2 of the logistic regression, it was not a significant predictor of obesity status. Similarly, when the age strata (18–34, 35–49, 50–65 years of age) × depressive subgroup interaction was used at step 2, it was not significantly associated with obesity status. These findings suggest that the observed differences in obesity rates by depressive subgroup

were similar in the 2 genders and across 3 different age strata from 18 to 65 years.

DISCUSSION

Using a large community database collected in the United States, the current study examined obesity rates in distinct vegetative subtypes of unipolar MDD and in nondepressed population controls. The results suggest that, in the United States, obesity rates based on the World Health Organization BMI cutoff of > 30 are highly elevated relative to controls in individuals with recent/current or past atypical depression, somewhat elevated in undifferentiated depression when depression has been active in the last 12 months, and similar to controls in classic depression. These results underline the importance of considering well-defined subgroups when studying comorbidity in heterogenous disorders, such as depression and obesity, and suggest that atypical depression is an important focus for future work in this area.

The current findings are highly consistent with the Virginia twin study,[16] which found a strong overlap in the heritability of atypical depression and obesity. In that study, twins with atypical depression weighed an average of 9 kg more than those with mild typical depression and 7.2 kg more than those with severe typical depression. Body mass indices were also substantially higher in the co-twins of twins with atypical depression. The authors concluded that "familial/genetic factors that influence the vulnerability to atypical depression also influence the vulnerability to obesity."[16(p397)] Hasler et al[22] followed a high-risk community sample in Switzerland between the ages of 19 and 40 years and found that atypical depression was associated with overweight defined as a BMI > 25 and with prospective weight gain between the ages of 20 and 40 years. The current results extend these findings by linking atypical depression with BMIs in the clinically obese range and by finding a consistent link between atypical depression and obesity across various age strata from 18 to 65 years of age.

Given that atypical depression is associated with distinct demographic, clinical, and etiologic factors relative to melancholic depression,[8–12] the current results have several important implications for future work in this area. For example, several authors have highlighted the importance of increased hypothalamic-pituitary-adrenal-axis activity as a major focus for depression/obesity work.[23–25] While this focus is most helpful when studying melancholic and/or hypercortisolemic depression and metabolic dysfunction, it should be noted that low to normal rather than high cortisol levels have frequently been demonstrated in atypically depressed patients.[9,26–29] These latter findings, combined with the current results, suggest that other processes relating eating behavior to mood also merit evaluation in depression-obesity work. Emotional eating, food reward processes, and altered brain monoamine activity have been implicated in this way.[30–35] Studying whether food is used to temporarily improve mood in the context of insecure interpersonal attachments, psychosocial adversity, and emotional dysregulation in atypical depression may also be of particular interest going forward.[12,36–39]

There are several limitations to the current project. First, while the NESARC database provides the information necessary to derive well-established neurovegetative subgroups of major depression, it was not designed for this purpose. However, the demographic and clinical correlates of atypical and melancholic depression that we found were entirely consistent with prior findings.[16–19]

Second, while our data suggest that classic depression is not associated with an elevated (World Health Organization–defined) obesity rate relative to the population-at-large, classic/hypercortisolemic depression may associate with the visceral subtype of obesity independently of BMI.[24,40] Further to this point, simple measures of BMI correlate only modestly with computerized tomography–based measures of visceral obesity.[41,42] Ideally, future studies should include not only depressive subtyping but also obesity subtyping based on objective data. The current results do suggest that identifying obesity comorbidity in subjects with classic depression should not be based on simple BMI measures.

As is always the case with cross-sectional designs, we cannot ascertain the direction of causality as it relates to the reported comorbidity rates. Obesity can precede the onset of depression in many cases,[7,43] and could in some way establish vulnerability to atypical more so than classic depression. While this developmental route is theoretically possible, at least one longitudinal follow-up study would suggest that atypical depression is more likely to precede obesity than to follow it.[22]

In conclusion, almost all previous studies of obesity-depression comorbidity have treated major depression as a unitary diagnosis. The current investigation found a robust link between atypical (but not classic) depression and obesity, independent of gender, age grouping, and whether depression was active in the past year. While classic depression was not associated with elevated obesity rates relative to controls, a specific focus on ventral obesity will be needed to address this issue more directly. Taken as a whole, the current results highlight the need to carefully consider both depression and obesity subtypes in comorbidity work going forward.

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