Are Mood Disorders and Obesity Related? A Review for the Mental Health Professional

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Objective: We reviewed evidence regarding a possible relationship between mood disorders and obesity to better inform mental health professionals about their overlap.

Method: We performed a MEDLINE search of the English-language literature for the years 1966–2003 using the following terms: *obesity*, *overweight*, *abdominal*, *central*, *metabolic syndrome*, *depression*, *mania*, *bipolar disorder*, *binge eating*, *morbidity*, *mortality*, *cardiovascular*, *diabetes*, *cortisol*, *hypertriglyceridemia*, *sympathetic*, *family history*, *stimulant*, *sibutramine*, *antiobesity*, *antidepressant*, *topiramate*, and *zonisamide*. We evaluated studies of obesity (and related conditions) in persons with mood disorders and of mood disorders in persons with obesity. We also compared studies of obesity and mood disorders regarding phenomenology, comorbidity, family history, biology, and pharmacologic treatment response.

Results: The most rigorous clinical studies suggest that (1) children and adolescents with major depressive disorder may be at increased risk for developing overweight; (2) patients with bipolar disorder may have elevated rates of overweight, obesity, and abdominal obesity; and (3) obese persons seeking weight-loss treatment may have elevated rates of depressive and bipolar disorders. The most rigorous community studies suggest that (1) depression with atypical symptoms in females is significantly more likely to be associated with overweight than depression with typical symptoms; (2) obesity is associated with major depressive disorder in females; and (3) abdominal obesity may be associated with depressive symptoms in females and males; but (4) most overweight and obese persons in the community do not have mood disorders. Studies of phenomenology, comorbidity, family history, biology, and pharmacologic treatment response of mood disorders and obesity show that both conditions share many similarities along all of these indices.

Conclusion: Although the overlap between mood disorders and obesity may be coincidental, it suggests the two conditions may be related. Clinical and theoretical implications of this overlap are discussed, and further research is called for.

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Whether or not mood disorders and obesity are related has been a focus of scientific debate for over 50 years.[1–13] Unfortunately, a recent comprehensive review of obesity for mental health professionals did not address this controversy.[14] However, in a recent review of "obesity-depression associations in the population," Faith et al.[15] concluded that there were "likely multiple obesity-depression covariations in the population, rather than a single pattern of association"(p. 935) and that there was need for "greater collaboration between depression and obesity specialists."(p. 935)

Many emerging lines of evidence suggest that reexamination of a potential relationship between mood disorders and obesity is in order, particularly for mental health professionals. In this regard, the significant overlap between mood disorders and obesity in clinical populations may be the most important. Weight gain, overweight, and obesity frequently complicate the treatment of mood disorders.[16–21] Conversely, depressive symptoms and mood disorders are common in persons of all ages seeking treatment for obesity,[13,22–26] as well as some of the general medical conditions associated with obesity, such as type 2 diabetes,[27,28] coronary artery disease,[29–31] and cerebrovascular disease.[32,33] However, the reasons for this overlap are not understood.

First, iatrogenic factors likely play a role. Many of the drugs used to treat mood disorders are associated with weight gain,[14,34,35] whereas some of the drugs used to treat the general medical conditions that co-occur with obesity may induce mood symptoms.[36]

Second, both mood disorders[37–41] and obesity[14,42–44] are increasingly severe public health problems. Substantial evidence indicates obesity has increased in prevalence in children[44] and adults[42,43] in the general population from at

least the 1970s to the present. Birth cohort data suggest mood disorders may be becoming more prevalent in younger populations.[37–39,41] Thus, mood disorders and obesity may be co-occurring to a greater degree simply by chance alone.

Third, mounting family history, twin, and genetic data suggest that both mood disorders[38,45–47] and obesity[48–52] are polygenic, heterogeneous conditions. Since epidemiologic data have shown there may be "multiple obesity-depression covariations" in the population, mood disorders and obesity may share common inherited pathogenic factors.[15]

It is therefore unknown how much of the clinical overlap between mood disorders and obesity is due to iatrogenic factors, the chance co-occurrence of 2 common conditions, shared inherited pathogenic factors, or various combinations of these possibilities. A better understanding of this overlap would likely lead to improved treatment of the co-occurrence of mood disorders and obesity and possibly of the individual conditions.

METHOD

To more carefully explore the relationship between mood disorders and obesity, we surveyed the literature for studies of obesity (and the obesity-related conditions overweight, abdominal obesity, and the metabolic syndrome[14,53–55]) in mood disorders and, conversely, of mood disorders (and their related conditions) in obesity. We also searched for studies examining the phenomenology, psychiatric and general medical comorbidity, family history, biology, and pharmacologic treatment response of obesity and compared these studies with similar studies of mood disorders. We performed a MEDLINE search of the English-language literature for the years 1966–2003 using the following terms: *obesity*, *overweight*, *abdominal*, *central*, *metabolic syndrome*, *depression*, *mania*, *bipolar disorder*, *binge eating*, *morbidity*, *mortality*, *cardiovascular*, *diabetes*, *cortisol*, *hypertriglyceridemia*, *sympathetic*, *family history*, *stimulant*, *sibutramine*, *antiobesity*, *antidepressant*, *topiramate*, and *zonisamide*.

We review these studies and discuss some of the clinical and theoretical implications of the overlap between mood disorders and obesity.

RESULTS

Studies of Obesity in Mood Disorders

We found 15 studies of obesity or obesity-related conditions (e.g., overweight or abdominal obesity) in persons with syndromal mood disorders.[4,12,18–20,45,56–66] (We did not include studies of psychotropic-associated weight gain unless they also evaluated body weight status.) These were a comparison of rates of obesity across different depressive subtypes in a female twin registry,[45] 2 prospective studies of development of overweight or obesity in children and adolescents with major depressive disorder,[4,57] a prospective study of depression in a group of normal-weight and obese adults that also provided limited data on obesity in persons with depression,[12] a comparison of body mass index (BMI) between psychiatrically hospitalized and healthy U.S. armed forces personnel,[58] a prospective study of development of overweight in a cohort of young adults with mood disorders from Zurich, Switzerland,[59] 7 cross-sectional studies of overweight or obesity in adult mood disorder patients,[18–20,60–64] and 2 studies of visceral fat deposition in female patients with major depressive disorder.[65,66] We discuss these studies below. Of note, although 5 of these studies used community samples,[4,12,45,58,59] and 3 used prospective designs,[4,57,59] we found no large-scale psychiatric epidemiologic study that assessed both the full range of mood disorders and body weight (or other anthropometric measures) in its subjects. We also found no study of the metabolic syndrome in a mood disorder population.

In the first community study, Kendler et al.[45] analyzed depressive symptoms in a community-based registry of 1029 female twin pairs and concluded that depression consisted of at least 3 etiologically heterogeneous syndromes that were partially distinct with respect to clinical, longitudinal, and familial/genetic factors: mild typical depression, atypical depression, and severe typical depression. They found that twins with atypical depression were significantly more likely to be obese (BMI > 28.6; 28.9%) than those with mild typical depression (6.0%) or those with severe typical depression (3.1%). The rate of obesity in the twins as a group was not reported, and mania was not evaluated.

In the second community (and first prospective) study, Pine et al.[4] evaluated 644 adolescents in 1983 (mean age = 14 years) and again in 1992 (mean age = 22 years) to assess the relationship between major depressive disorder and conduct disorder in youth and obesity in early adulthood. Diagnoses were assessed in the 1992 evaluation with the Diagnostic Interview Schedule for Children (DISC); bipolar disorder was not determined. Univariate analyses showed that a higher BMI in adulthood was associated with increasing depressive and conduct symptoms in adolescence. Also, adulthood obesity was associated with adolescent depression in females, but not males, and with depression in adulthood in both genders. However, the latter association was positive in females and negative in males. Multivariate analyses showed that adulthood obesity was predicted by adolescent conduct disorder and the gender-by-adult depression interaction. Of note, the adolescent depression and conduct scores were significantly positively correlated.

In the third community (and second prospective) study, a longitudinal assessment of physical and mental health, Roberts et al.[9,11,12] evaluated 1886 survey respondents

who were aged 50 years or older from Alameda County, Texas, in 1994 and 1999. The Primary Care Evaluation of Mental Disorders (PRIME-MD) was used to assess whether subjects met DSM-IV criteria for a major depressive episode within the past 2 weeks; as in the previous 2 studies, mania was not assessed. Obesity (BMI ≥ 30) was associated with current major depression cross-sectionally, both in 1994 and 1999. Specifically, the prevalence ratio for obesity among those with depression was 1.65 with a 95% CI = 1.28 to 2.13. Depression in 1994 predicted obesity in 1999 (OR = 1.92; 95% CI = 1.31 to 2.80), but not after controlling for obesity in 1994 (OR = 1.32; 95% CI = 0.65 to 2.70). No other data regarding obesity in persons with depression were reported.

In the fourth community study, Wyatt et al.[58] compared the height, weight, and BMI of 7514 U.S. active duty military personnel hospitalized for bipolar disorder, major depressive disorder, or schizophrenia and 85,954 healthy subjects matched for date of service entry to evaluate the relationship between psychiatric illness and physique. No consistent differences in height, weight, or BMI were found between patients and controls or between patient groups. However, there was a diagnostic effect on BMI for white males: the mean BMI in patients with bipolar disorder was greater than the mean BMI in controls, which was equal to the mean BMI in patients with schizophrenia, which, in turn, was greater than the mean BMI in patients with major depressive disorder. A limitation of this study was that service entry criteria (including mental health and weight status) were not described.

In the second prospective study, Pine et al.[57] followed 2 age- and sex-matched groups of children 6 to 17 years old with major depression (N = 90) or no psychiatric disorder (N = 87) for 10 to 15 years with standardized psychiatric evaluations. Childhood major depression was found to be significantly positively associated with adulthood BMI, and this association persisted after controlling for age, gender, substance use, social class, pregnancy, and medication exposure. Specifically, the children with major depression had a higher mean BMI as adults (26.1) than the control children (24.2). Also, a bivariate logistic model showed that childhood depression predicted a 2-fold increase in risk for adult overweight status. Duration of depression between childhood and adulthood was associated with adult BMI, but this was not found for gender, change in eating patterns occurring with depressive episodes, diet, or medication use. Also, BMI did not differ between subjects who were or were not currently depressed at the time of the adult assessment.

In the fifth community (and third prospective) study, Hasler et al.[59] evaluated mood disorders in 591 young adults at ages 18 to 19 years from the general population of Zurich, Switzerland, and followed them until age 40 years. Nineteen percent were classified as overweight (which was not defined). Atypical depression was positively associated with overweight in males and females; hypomanic symptoms were associated with overweight only in males. These associations remained significant after controlling for medication, social, and educational variables.

The 7 cross-sectional studies of obesity in mood disorder patients are summarized in Table 1.[18–20,60–64] These studies are difficult to compare due to their different methodologies, including the use of different patient populations and different definitions of mood disorders and obesity. Thus, rates of obesity range from a low of 19% in male bipolar I patients from New Zealand[18] to a high of 67% in a group of mixed mood disorder patients of both genders from Germany.[60]

Of note are 4 studies that used comparison groups. Thus, in 1979, Muller-Oerlinghausen et al.[60] reported that 49 stable mood disorder patients receiving long-term lithium (29 of whom had bipolar disorder) had a significantly higher rate of "severe obesity" (BMI > 30; 12%) than the expected general population rate (5.7%). By contrast, in 1993 in Japan, Shiori et al.[62] compared the frequency distribution of body weight of 106 patients hospitalized for DSM-III major depression with that of a standard group and found that the patients' body weight distribution showed significantly more patients than expected in the underweight groups. This was particularly true for women. Also, there were significantly more patients with melancholia in the underweight groups than expected.

In 2000, Elmslie et al.[18] compared the prevalence of overweight, obesity, and abdominal obesity in 89 euthymic outpatients with bipolar I disorder (87% of whom were receiving pharmacologic maintenance treatment) to that of 445 age- and sex-matched community control subjects in New Zealand. Female patients had significantly higher prevalence rates of overweight (44% vs. 25%), obesity (20% vs. 13%), and abdominal obesity (59% vs. 17%) than female control subjects. Although there was no significant difference in the rates of overweight between male patients (29%) and control subjects (43%), male patients had significantly higher rates of obesity (19% vs. 10%) and abdominal obesity (58% vs. 35%).

In 2002, McElroy et al.[19] assessed the prevalence of overweight and obesity in 644 outpatients with bipolar disorder, types I and II, in both the United States and Europe; 57% of the total group was overweight or obese, with 31% overweight (BMI ≥ 25 but ≤ 29.9), 21% obese (BMI ≥ 30 but ≤ 39.9), and 5% extremely obese (BMI ≥ 40). Rates of overweight, obesity, and extreme obesity in the American patients were then compared with the most concurrent American population estimates of body weight status available (those of the Third National Health and Nutrition Examination Survey [NHANES III]). Female bipolar patients had higher rates of obesity and extreme obesity, but lower rates of overweight, than reference women. Male bipolar patients had higher rates

Table 1. Clinical Studies of Obesity (and related weight disorders) in Patients With Mood Disorders

Study	Patients	Definition of Weight Categories	Findings
Muller-Oerlinghausen et al[60]	49 patients with bipolar disorder (N = 26), major depression (N = 14), schizoaffective disorder (N = 8), and unclassified (N = 1)	Obesity for females: BMI = 24–30; obesity for males: BMI = 25–30; severe obesity: BMI > 30	33 (67%) were obese (43%) or severely obese (24%)
Berken et al[61]	40 outpatients with major depression	Not provided	25% were obese prior to TCA therapy
Shiori et al[62]	106 Japanese inpatients with DSM-III major depression	Not provided	Patients' body weight distribution on admission had significantly more individuals in the underweight groups compared with a standard distribution from the general population. Also, more patients with melancholia were in the underweight groups than expected. Rates of patients in body weight categories were not provided
Elmslie et al[18,63]	89 euthymic outpatients with bipolar I disorder from New Zealand; 445 community controls	Overweight: BMI ≥ 25 but ≤ 29.9; obesity: BMI ≥ 30; abdominal obesity: WHR > 0.8 for females and > 0.9 for males	Female patients had significantly higher prevalence rates of overweight (44% vs 25%), obesity (20% vs 13%), and abdominal obesity (59% vs 17%); male patients had significantly higher rates of obesity (19% vs 10%) and abdominal obesity (58% vs 35%)
McElroy et al[19]	644 outpatients from U.S. and Europe with DSM-IV bipolar I and II disorders	Overweight: BMI ≥ 25 but ≤ 29.9; obesity: BMI ≥ 30 but ≤ 39.9; extreme obesity: BMI ≥ 40	57% were overweight or obese, with 31% overweight, 21% obese, and 5% extremely obese
Fagiolini et al[64]	50 outpatients with DSM-IV bipolar I disorder	Overweight: BMI ≥ 25 but ≤ 29.9; obesity: BMI ≥ 30	34 (68%) were overweight (36%) or obese (32%)
Fagiolini et al[20]	175 outpatients with DSM-IV bipolar I disorder	Obesity: BMI ≥ 30	62 (35%) were obese

Abbreviations: BMI = body mass index, TCA = tricyclic antidepressant, WHR = waist-hip ratio.

of overweight and obesity, but not extreme obesity, than reference men.

Several of the cross-sectional studies evaluated correlates of overweight and obesity in patients with bipolar disorder.[18–21,63,64] In the 89 euthymic bipolar outpatients evaluated by Elmslie et al.,[18,63] significantly more patients receiving antipsychotic medications were obese compared with patients not receiving these agents. Patients also reported a significantly higher total daily sucrose intake, percentage of energy derived from carbohydrates, total fluid intake, and intake of sweetened beverages, as well as significantly fewer episodes of physical activity, compared with reference subjects. In the group of 644 bipolar patients evaluated by McElroy et al.,[19] significant associations were found among the weight categories overweight, obesity, and extreme obesity and the variables age, annual income, comorbid binge-eating disorder, hypertension, arthritis, type 2 diabetes, exercise habits, and coffee consumption.

In a group of 50 bipolar I patients receiving lithium-based treatment, Fagiolini et al.[64] found that patients who were overweight or obese (68% of the sample) had significantly more previous depressive episodes compared with patients who were normal weight (30% of the sample) or underweight (2%). In a larger sample of 175 consecutive bipolar I patients receiving acute and long-term lithium-based treatment (35% of whom were obese), Fagiolini et al.[20] reported that, compared with nonobese patients, obese patients had significantly fewer years of education, more previous depressive and manic episodes, and higher baseline Hamilton Rating Scale for Depression (HAM-D) scores and required more time in acute treatment to achieve remission. A similar percentage of obese (N = 46, 74%) and nonobese (N = 79, 70%) subjects completed acute treatment. During maintenance treatment, however, significantly more obese patients experienced a recurrence (N = 25, 54%) as compared with those who were not obese (N = 28, 35%). Also, the time to recurrence was significantly shorter for patients who were obese at baseline. When recurrence type was examined, the percentage of patients experiencing depressive recurrences was significantly greater for obese patients (N = 15, 33%) than for nonobese patients (N = 11, 14%).

In the first of 2 studies that evaluated intra-abdominal fat deposition in mood disorder patients, Thakore et al.[65] compared the body fat distribution (measured by abdominal computed tomography [CT]) of 7 medication-free women (mean age = 36.6 years; mean BMI = 24.4) with DSM-III-R major depression, melancholic subtype, with that of 7 healthy control women (mean age = 32.7 years;

Table 2. Theoretical Relationships Between Mood Disorders and Weight Disorders[a]

Mood Disorder	Associated Weight Disorder
Major depressive disorder	Underweight, overweight, obesity
Atypical features	Overweight, obesity
Typical (melancholic) features	Underweight, abdominal obesity
Juvenile onset	Overweight, obesity
Bipolar disorder	Abdominal obesity, overweight, obesity

[a]Based on data from studies of obesity and related conditions in persons with syndromal mood disorders.*

mean BMI = 23.6). None of the women had a history of obesity. Patients and controls did not differ regarding weight, BMI, waist-hip ratio (WHR), and total body fat, but patients had significantly greater intra-abdominal fat stores than controls. In addition, patients had significantly higher baseline cortisol levels than controls, and intra-abdominal fat stores correlated with both WHRs and cortisol levels.

In the second study, Weber-Hamann et al.[66] compared intra-abdominal fat stores (also measured by abdominal CT) in 22 postmenopausal women (mean age = 65.1; mean BMI = 24.5) with DSM-IV major depressive disorder and 23 healthy control women (mean age = 64.0; mean BMI = 24.3). Visceral fat stores did not differ between the depressed patients as a group and the healthy controls or between the hypercortisolemic depressed patients and the controls. However, hypercortisolemic depressed patients showed greater visceral fat stores than normocortisolemic depressed patients.

Taken together, these studies suggest that some subtypes of mood disorder may be associated with overweight or obesity, whereas other subtypes may be associated with underweight (Table 2). Mood disorder subtypes associated with overweight or obesity may include major depressive disorder with atypical features,[45,59] major depressive disorder with juvenile onset,[4,57] and bipolar disorder, especially when depressive features predominate.[18–20,59,60,63,64] Subtypes associated with underweight may include major depressive disorder with typical[45] or melancholic features.[62] Moreover, major depressive disorder with hypercortisolemia, even when associated with normal body weight, may be associated with visceral fat deposition.[65,66] Finally, prospective studies[4,57,59] suggest onset of mood disorder may precede development of overweight or obesity in some persons, especially patients with juvenile-onset major depression[57] and young females in the community with major depression.[4,59] However, these conclusions are preliminary and need to be verified in epidemiologic and longitudinal studies using validated assessments of both mood disorders and anthropometric measures.

Clinical Studies of Mood Disorders in Obesity

We found numerous studies that assessed some aspect of mood pathology in obese persons seeking weight loss treatment.[2,3,13,22–26,67–94] Although most of these studies assessed mood, particularly depressive symptoms, using clinical interviews, self-report scales, or psychological tests (see Phenomenology),† 12 studies assessed syndromal mood disorders using operational diagnostic criteria (Table 3).‡ The rates of mood disorders in these studies ranged from a low of 8%[74] to a high of 60%,[80] with a weighted average of 32% (see Table 3). Seven of these studies also used clinician-administered structured diagnostic interviews to assess syndromal mood disorders[22,25,80,82,83,86,94]; 183 (41%) of 446 patients met criteria for lifetime mood disorders in these studies compared with 111 (24%) of 461 patients in the 5 studies that did not use structured clinical interviews[74,75,77,79,88] (see Table 3).

Most of the studies that assessed syndromal mood disorders did not use control groups; such studies can overestimate comorbidity due to Berkson's bias.[8] When we restricted our search to those studies that specifically used normal-weight or general medical control groups, as well as operationalized diagnostic criteria and clinician-administered structured interviews to assess mood disorders, we found only 2 such studies.[22,25] Both found significantly elevated rates of mood disorders in obese patients compared with normal-weight controls.

In the first study, Black et al.[22] found significantly higher rates of major depression (19% vs. 5%) and any mood disorder (31% vs. 9%) by DSM-III criteria in 88 consecutive morbidly obese patients seeking bariatric surgery compared with 76 normal weight controls. Four (4.5%) of the obese patients had lifetime mania or atypical bipolar disorder compared with none of the control subjects.

In the second study, Britz et al.[25] found that 20 (43%) of 47 adolescents and young adults receiving inpatient treatment for extreme obesity (mean BMI = 42.4) met DSM-IV criteria for a mood disorder, compared with 8 (17%) of 47 obese controls (mean BMI = 29.8) and 247 (15%) of 1608 general population controls. Among the obese patients, 14 (30%) had a depressive disorder (11 with major depression and 3 with dysthymia) and 5 (11%) had a bipolar disorder (1 with bipolar I and 4 with bipolar II). (Rates of mood disorder between the obese population controls and the general population controls did not differ; see Community Studies of Mood Disorders in Obesity.) Because the mean BMI of the obese patient group was significantly higher than that of the obese population controls, it could not be determined if the higher rate of mood disorder in the patient group was related to their extreme obesity or their treatment-seeking behavior.

*References 4, 18–20, 45, 57, 59, 60, 62–64.
†References 13, 23, 26, 67–73, 76, 78, 81, 84, 85, 87, 89–93.
‡References 22, 25, 74, 75, 77, 79, 80, 82, 83, 86, 88, 94.

Table 3. Rates of Mood Disorders Defined by Diagnostic Criteria in Obese Patients[a]

Study	Clinical Population	Definition of Obesity	Psychiatric Diagnostic Criteria	Findings
Wise and Fernandez[74]	24 persons seeking ileal bypass	Massive: mean weight = 342 lbs; averaged 232% of expected weight	Feighner et al	2 (8%) had "secondary" affective disorder
Halmi et al[75]	80 persons who had gastric bypass operations	Severe: mean weight ≥ 236% of ideal body weight at surgery	DSM-III	23 (29%) had a depressive disorder
Hopkinson and Bland[77]	73 females seeking intestinal bypass surgery	Gross: ≥ 100 lb above or double ideal body weight	Feighner et al	14 (19%) had a primary depressive disorder
Gertler and Ramsey-Stewart[79]	153 persons seeking bariatric surgery	Morbid: ≥ 80% above ideal body weight	DSM-III	35 (23%) had an affective disorder
Hudson et al[80]	70 obese females recruited for an obesity treatment study	Mild (20%) Moderate (67%) Severe (13%)	DSM-III[b]	42 (60%) had a major affective disorder
Marcus et al[82]	50 subjects recruited for an obesity treatment study (fluoxetine)	BMI ≥ 30	DSM-III[b]	10 (20%) had an affective disorder; 7 had major depression and 3 had dysthymia
Black et al[22]	88 persons seeking vertical banded gastroplasty	Morbid: 100% or 100 lb over ideal body weight	DSM-III[b]	27 (31%) had an affective disorder; 17 (19%) had major depression, 7 (8%) had dysthymia, 3 (3%) had mania, and 1 (1%) had atypical bipolar disorder
Goldsmith et al[83]	54 subjects presenting for an obesity treatment study (fluoxetine and CBT)	BMI ≥ 30; mean BMI = 40	DSM-III-R[b]	26 (48%) had a lifetime mood disorder; 3 (6%) had bipolar disorder
Specker et al[86]	100 women presenting for weight loss treatment	Mean BMI = 36 (range, 26–44)	DSM-IV[b]	38 (38%) had a lifetime mood disorder; 35 (35%) had lifetime major depression
Powers et al[88]	131 persons presenting for gastric restriction surgery	Mean BMI = 53	DSM-IV	37 (28%) had a lifetime mood disorder
Britz et al[25]	47 adolescents and young adults receiving inpatient treatment	Extreme: mean BMI = 42	DSM-IV[b]	20 (43%) had a lifetime mood disorder; 14 (30%) had a depressive disorder and 5 (11%) had a bipolar disorder
Hsu et al[94c]	37 persons awaiting gastric bypass surgery	Extreme: mean BMI = 50	DSM-IV[b]	20 (54%) had lifetime major depression

[a]For all studies combined, 32% of patients (294 of 907) had a lifetime mood disorder. In studies that used structured clinical interviews to assess syndromal mood disorders, 41% of patients (183 of 446) had lifetime mood disorders, compared with 24% of patients (111 of 461) in studies that did not use structured clinical interviews.
[b]Mood disorders evaluated with a clinician-administered structured diagnostic interview.
[c]Only 15% of eligible subjects were accepted into the study.
Abbreviations: BMI = body mass index (mg/kg^2), CBT = cognitive-behavioral therapy.

Community Studies of Mood Disorders in Obesity

We found numerous studies that assessed symptoms of depression, anxiety, distress, or stress in community populations of persons with obesity, overweight, abdominal obesity, or the metabolic syndrome (see Phenomenology).[5,6,8–12,23,25,95–123] However, only 5 of these studies used operational diagnostic criteria to assess syndromal mood disorders in community samples with obese or overweight persons.[8,9,11,12,25,121,123] One study found both a positive and a negative relationship between obesity and major depressive disorder[8]; 2 studies (1 of which is represented by 3 reports) found only a positive relationship[9,11,12,123]; 1 study found a possible positive relationship[121]; and 1 study found no relationship between obesity and any mood disorder.[25]

In the largest study, Carpenter et al.[8] used the Alcohol Use Disorders and Associated Disabilities Interview Schedule to assess the relationships among weight, obesity, suicide ideation and attempts, and past-year DSM-IV major depressive disorder in 40,086 national survey respondents aged 18 years and older. Bivariate analysis of weight data showed that BMI was significantly associated with DSM-IV major depressive disorder via a U-shaped relationship, such that relatively high and low BMI values were associated with an increased probability of major depression. The unadjusted analyses of weight status showed that, compared with average-weight respondents (BMI ≥ 20.78 and ≤ 29.99), obese respondents (BMI ≥ 30) had increased odds of suicide ideation (but not of major depressive disorder or suicide attempts), whereas underweight respondents (BMI < 20.77) had increased odds of major depressive disorder and suicide ideation. Adjusted analyses, however, showed that the relationship between weight and depression was affected by gender. Among women, increased BMI was associated with both major depressive disorder and suicide ideation. Among men, decreased BMI was associated with major depressive disorder, suicide attempts, and suicide ideation. Similarly, relative to average weight, obesity was

associated with increased odds of past-year major depressive disorder among women (OR = 1.37; 95% CI = 1.09 to 1.73) but decreased odds of past-year major depressive disorder among men (OR = 0.63; 95% CI = 0.60 to 0.67). Furthermore, relative to average weight, underweight was associated with increased odds of suicide ideation and suicide attempts in men but not women.

In the second largest study, Onyike et al.[123] randomly evaluated 8410 persons aged 15 to 39 years from the NHANES III with the Diagnostic Interview Schedule. Obesity (BMI ≥ 30) was associated with past-month DSM-III major depression in women (OR = 1.82, 95% CI = 1.01 to 3.3) but not in men (OR = 1.73, 95% CI = 0.56 to 5.37). However, severe (class 3) obesity (BMI ≥ 40) was associated with past-month depression in women (OR = 3.78, 95% CI = 1.64 to 8.68) and men (OR = 7.68, 95% CI = 1.03 to 57.26).

In the third largest study (as discussed earlier), Roberts et al.[9,11,12] evaluated 1886 survey respondents, aged 50 years and older, from Alameda County, Texas, in 1994 and 1999, with the PRIME-MD to determine whether subjects met current DSM-IV criteria for a major depressive episode. Obesity (BMI ≥ 30) was associated with current major depressive episodes in both 1994 and 1999. Specifically, the prevalence ratio for depression among the obese was 1.83 (95% CI = 1.33 to 2.53). In addition, obesity in 1994 was associated with increased risk of depression in 1999, even after controlling for depression at baseline (OR = 2.01, 95% CI = 1.25 to 3.25). Unlike the Carpenter et al. study[8] or the Onyike et al. study,[123] no gender differences were found in the relationship between obesity and depression.

In the study that found a possible positive relationship, Bulik et al.[121] reported that 34% of 169 obese (self-reported BMI ≥ 30) women from a community sample of female twins met criteria for lifetime DSM-III-R major depression as assessed with a modified version of the Structured Clinical Interview for DSM-III-R. The rate of major depression for the entire sample was not provided.

In the negative study (as discussed earlier), Britz et al.[25] compared rates of DSM-IV mood (depressive and bipolar) disorders, assessed with the Munich-Composite International Diagnostic Interview (M-CIDI), among a clinical group of 47 extremely obese adolescent and young adult inpatients (mean BMI = 42.4), 47 gender-matched population-based obese controls (mean BMI = 29.8), and a population-based control group of the same age range (N = 1608; 788 males). Although the rate of mood disorders was significantly higher in the clinical group (42.6%) than in both control groups, there was no difference in the rates of mood disorders between the population-based obese control subjects (17.0%) and the population controls (15.4%).

We found no studies of syndromal mood disorders in abdominal obesity or the metabolic syndrome. However, 11 studies assessed mood symptoms with standardized measures in community samples of persons with abdominal obesity (N = 10)* or the metabolic syndrome (N = 1).[114] In 8 studies, abdominal obesity, determined by WHR, was associated with depressive symptoms in men (N = 3),[113,114,120] women (N = 3),[6,105,106] or both.[116,122] In 5 studies, the association with depressive symptoms was stronger for abdominal obesity (WHR) than for general obesity (BMI).[6,105,106,113,120]

In short, the most methodologically sound clinical studies of mood disorders in obesity found a positive relationship between general obesity (especially severe obesity) and both major depressive disorder and bipolar disorder in females and males.[22,25] The 3 largest of the 5 community studies of mood disorders in obesity found a positive relationship between general obesity and major depressive disorder in women,[8,9,11,12] but both a negative[8] and positive[9,11,12,123] relationship in men. In one of the latter studies, however, the positive relationship in men was seen only in severe obesity.[123] The 2 smaller community studies were possibly positive[121] and negative,[25] respectively, regarding a relationship between obesity and mood disorders. Finally, some,† but not all,[5,108,115] community studies found a positive relationship between abdominal obesity and depressive symptoms in men and women.

The disparate results of these studies are difficult to explain, but may be due to methodological differences among studies as well as to differential effects of various factors, and the interactions among these factors, on the relationship between obesity and mood disorders. For example, age may affect the relationship between obesity and mood disorder. Thus, 2 of the prospective studies of obesity in mood disorder[4,8] discussed earlier found positive relationships between depression in youth and overweight in early adulthood (one in females only[4]), whereas the 1 prospective study of depression in obesity[9,11,12] found that depression in late adulthood did not predict obesity in later adulthood (but only after controlling for obesity at baseline). Moreover, gender's effect on obesity and mood disorder may be affected by age. Thus, gender effects were found in the Carpenter et al.[8] study, which included subjects aged 18 years and older, and in the Onyike et al. study,[123] which included subjects aged 15 to 39 years, but not in the Roberts et al.[9,11,12] study, which included subjects ages 50 years and older. Further research is clearly needed.

Phenomenology

Obesity and mood disorder share several important phenomenologic features, particularly abnormalities in

*References 5, 6, 105, 106, 108, 113, 115, 116, 120, 122, 123.
†References 6, 105, 106, 113, 114, 116, 120, 122.

appetite, eating behavior, and physical activity. Thus, for obesity, numerous clinical and community studies have consistently described increased appetite, overeating, and reduced physical activity in obese subjects.* (Although a subset of obese persons have reported that their eating behavior and physical activity were normal, or that they ate very little, modern studies have documented that obese persons of all ages eat more and are less physically active than their lean counterparts.[48,126]) Moreover, although important exceptions exist,† many of the clinical studies and some of the community studies that assessed depressive symptoms with standardized measures found elevated rates of depressive symptoms in the obese groups compared with the normal weight or general medical clinical controls[23,24,26,70,71,81,87] or with the nonobese community controls.‡

For mood disorders, it is well established that depressive and manic syndromes are associated with anorexia, hypophagia, hyperactivity, and weight-loss factors associated with underweight.[38,45,127] However, clinical[16,38,127,128] and community[45,129–131] studies have shown that a substantial portion of persons with depressive syndromes have increased appetite, overeating, reduced physical activity, and weight gain—so-called reversed neurovegetative or atypical features of depression.[132] Indeed, several subtypes of depression have been delineated, in part, because of their association with these symptoms. These include atypical depression,[45,128–132] somatic depression,[133] seasonal affective disorder,[134] and perimenstrual depression.[135] Growing research has shown that these symptoms are common, distinct, and clinically relevant among patients with depressive syndromes.[45,128–132] They have been associated with female preponderance, earlier onset, greater duration, subthreshold bipolar disorder, familial aggregation, biological differences, and preferential response to monoamine oxidase inhibitors over tricyclic antidepressants.

Unfortunately, we were unable to find any studies that specifically examined reversed neurovegetative depressive features in obesity. Conversely, very few studies have evaluated the relationship between reversed neurovegetative features and actual body weight in mood disorders. Nonetheless, preliminary data suggest that atypical depressive symptoms are more likely to be associated with overweight than are typical depressive symptoms. In 2 recent latent class analyses of depressive symptoms from 2 different population-based twin registries, Kendler et al.[45] and Sullivan et al.[131] each found that the "atypical" classes, characterized primarily by increased appetite and weight gain, and to a lesser extent psychomotor retardation, had significantly higher self-reported BMIs than the "typical" classes.

Course of Mood Symptoms and Weight Change

We found 5 community studies that prospectively examined the relationship between mood symptoms and weight change. Hällström and Noppa[101] studied 800 women from the community, 38 to 54 years of age, and found no relationship between obesity and "depth of depression" upon cross-sectional analysis. However, 6 years later,[136] women who had gained ≥ 5 kg had significantly higher baseline HAM-D scores than those who had gained < 5 kg. DiPietro et al.[137] assessed the effect of depressive symptoms on weight in 1794 adults, aged 25 to 74 years, from 1971 to 1975 and from 1982 to 1984. Overall, younger adults (< 55 years) gained weight, whereas older adults (≥ 55 years) lost weight. Depression at baseline was associated with additional weight gain in younger men but a reduction in weight gain in younger women. Among older men and women, depression was associated with additional weight loss.

Barefoot et al.[138] assessed the relationship between depressive symptoms (assessed with the Minnesota Multiphasic Personality Inventory [MMPI]) and weight change in 3560 college students in the mid-1960s and again in the late 1980s and found a statistically significant interaction between depression status and baseline BMI. Depressed participants who were initially lean gained less weight than lean participants who were not depressed. Conversely, depressed participants who were initially heavy gained more weight than heavy participants who were not depressed.

Goodman and Whitaker[10] evaluated a cohort of 9374 adolescent girls in grades 7 through 12 in 1995 and 1 year later to determine whether depressed mood predicted the development and persistence of obesity in adolescence. Depressed mood was defined as a score of ≥ 24 for females and ≥ 22 for males on the Center for Epidemiologic Studies Depression Scale, and obesity was defined as BMI ≥ 95th percentile. After controlling for various factors (age, race, gender, parental obesity), the authors found that baseline depressed mood predicted obesity at 1-year follow-up among subjects who were obese at baseline as well as those who were not obese. However, baseline depression did not correlate with baseline obesity. Also, baseline obesity did not predict follow-up depression.

In sum, these studies suggest that depressive symptoms may be associated with long-term weight gain[101,136] and obesity,[10] as well as long-term weight loss.[137] These studies also show that the relationship between depressive symptoms and weight gain[101,136] or obesity[10] may appear prospectively but not cross-sectionally in the same cohort of persons[10,101,136] and that the relationship between depressive symptoms and weight over time may be affected by age.[137]

*References 23, 43, 48, 97, 111, 124, 125.
†References 68, 95, 97, 99–101, 104, 112.
‡References 8, 98, 103, 107, 110, 116–119.

Comorbidity

We found 2 areas of comorbidity where obesity and mood disorders have each received relatively extensive study. These were co-occurrence with eating disorders and with general medical disorders.

Comorbidity of obesity and mood disorders with binge eating, bulimia nervosa, and binge-eating disorder. Considerable evidence indicates that obesity and mood disorders may each be related to binge-eating behavior in general, as well as DSM-IV–defined bulimia nervosa and binge-eating disorder. Thus, obesity,[139–148] major depressive disorder,[144–151] and hypomania[152,153] have each been shown to co-occur with binge-eating behavior, bulimia nervosa, and/or binge-eating disorder in community samples. Also, clinical and community studies have found significantly higher rates of mood disorders in obese persons with binge-eating behavior or binge-eating disorder compared with obese persons without binge eating.[80,81,86,122,140] Indeed, one potential relationship between obesity and mood disorders has been hypothesized to be mediated via shared relationship with binge eating.[15,140]

Morbidity and mortality of obesity and mood disorders. Obesity and mood disorders also share similarities with respect to general medical comorbidity. Thus, general obesity,[14,43,53,154–156] abdominal obesity,[53–55,154,156,157] and depressive symptoms and/or major depressive disorder[27–33,158–161] have each been associated with elevated morbidity from cardiovascular disease, hypertension, and type 2 diabetes in community studies. Bipolar disorder has been associated with increased rates of type 2 diabetes in clinical studies.[162–164] In addition, general obesity,[165,166] abdominal obesity,[156] the metabolic syndrome,[167] depressive disorders,[168–170] and bipolar disorder[168,169] have each been associated with increased mortality in community studies, including from coronary heart disease, stroke, type 2 diabetes, and cancer. Indeed, epidemiologic studies have suggested that obesity, abdominal obesity, the metabolic syndrome, depressive symptoms, and major depressive disorder are all independent risk factors for hypertension, coronary heart disease, stroke, and type 2 diabetes. Of note, unlike most of the studies of the morbidity of obesity (and obesity-related conditions), which usually did not control for the presence or absence of depression, some of the studies of morbidity of depression controlled for the presence or absence of obesity. The latter studies generally found that the relationship between depression and cardiovascular morbidity persisted even when obesity was controlled for.[160,161] Nonetheless, the relationship between mood disorders and obesity as risk factors for general medical comorbidity has not been fully explored. Interestingly, mechanisms by which both conditions have been hypothesized to increase morbidity and mortality from cardiovascular disease include poor self-care (e.g., impaired dietary and exercise habits), increased platelet aggregation, low-grade systemic inflammation, and a common relationship with the metabolic syndrome (see Biology).[7,29]

Family History

Adoption and twin studies have shown that heritable factors contribute substantially to the familiality of both obesity[48–51] and mood disorders.[38,45–47] Although we found no controlled studies of obesity in the family members of probands with mood disorders, we found 2 latent class analyses of depressive symptoms of 2 separate community-based twin registries (one entirely female-female twin pairs[45] and the other male-male and male-female twin pairs[131]) that also assessed self-reported BMIs. Both analyses showed that, compared with co-twins in the nonclinical classes, atypical depressive symptoms (characterized primarily by increased appetite and weight gain) in one twin were significantly positively associated with self-reported BMI in the co-twin. In the all-female registry,[45] mild typical depressive symptoms in one twin were also significantly associated with elevated BMI in the co-twin, but this increase was about half as large as seen in the co-twins with atypical depression.

We found only 1 controlled family history study of mood disorders in obese probands. Black et al.[171] evaluated 88 morbidly obese gastroplasty patients and a healthy comparison group using the family history method and Family History-Research Diagnostic Criteria (FH-RDC). Obese patients were significantly more likely than controls to have first-degree relatives with depression (18% vs. 4%) and bipolar disorder (3% vs. 0%). Although extremely preliminary, taken together, these findings suggest that obesity and mood disorders, or more precisely, certain types of obesity and certain types of mood disorder, may share common heritable pathogenic factors.

Biology

No studies, to our knowledge, have directly compared the biology of obesity (or an obesity-related disorder) with that of a mood disorder. Although an extensive review comparing the biology of obesity with that of mood disorders is beyond the scope of this article, it is noteworthy that a number of biological systems have received fairly extensive study in both conditions. Many of these studies were limited by the fact that either mood (in the obesity studies) or weight (in the mood disorder studies) was not controlled for. Nonetheless, biological abnormalities found in both obesity and mood disorders have included indications of dysregulation of the hypothalamic-pituitary-adrenocortical (HPAC) axis[132,172–176] and of the central serotonin, norepinephrine, and dopamine neurotransmitter systems.[176–179] Interestingly, the profile of HPAC dysregulation found in obesity, particularly abdominal obesity,[172–175] has been more similar to that seen in atypical than in melancholic depression.[132] Other ab-

normalities found in both obesity and mood disorders have included elevated serum leptin levels,[180–182] low-grade systemic inflammatory changes (e.g., elevated C-reactive protein),[183,184] and glucose and lipid metabolic abnormalities. The latter have included insulin resistance,[53,55,185–189] hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol (but with no evidence of increased low-density lipoprotein [LDL] or total cholesterol in mood disorders),[54,190] and (as mentioned earlier) increased intra-abdominal fat deposition.[55,65,66]

Of note, although the cause of abdominal visceral fat deposition in obesity and depression is unknown, it has been hypothesized to be due in part to HPAC dysfunction in both conditions.* The HPAC dysfunction of abdominal visceral fat deposition in obesity, in turn, has been attributed to the effects of psychosocial stress or to symptoms of depression and anxiety.[122,172,191] Indeed, depressive symptom measures have been shown to correlate with metabolic abnormality measures in the metabolic syndrome and related conditions. In a study of 90 middle-aged men with the "insulin resistance syndrome," high levels of "vital exhaustion and anger out" correlated with increased WHR as well as an augmented mean insulin response during an oral glucose tolerance test, increased triglyceride levels, and decreased HDL cholesterol levels.[114] Similarly, in a study of depression and biochemical correlates in women with polycystic ovary syndrome, an endocrine disorder frequently characterized by obesity and insulin resistance, depressive symptoms were positively associated with higher BMI and greater insulin resistance.[192] Such data have led some authorities to suggest that the metabolic syndrome and depression may be related.[7]

Response to Pharmacotherapy

We found no studies that compared the pharmacologic treatment of obesity with that of a mood disorder. However, certain pharmacologic agents have been studied in both conditions. Review of these studies suggests both similarities and differences in the pharmacologic treatment response of both conditions.

Studies of antiobesity agents in mood disorders. Stimulants, such as amphetamine and methylphenidate, which are effective in inducing weight loss but are no longer approved for obesity because of their abuse potential,[193] have been the most extensively studied centrally active antiobesity agents in depression.[194–196] Although many of the trials have limitations, taken together, they suggest stimulants are not effective in many patients with major depression.[195] However, limited controlled data suggest stimulants may be helpful in some depressed populations.[194,196] Thus, stimulants have been shown to be superior to placebo in reducing anxious-depressive symptoms in obese patients[197] and in treating depression associated with medical illness.[198] There also have been reports of successful use of stimulants to augment antidepressants in treatment-resistant and treatment-refractory patients.[196]

We were unable to find published controlled trials of other centrally acting antiobesity agents in mood disorders. However, preliminary data suggest that some of these agents may have antidepressant properties. The serotonergic agents fenfluramine and dexfenfluramine (which have been removed from the market for safety concerns)[199] have been reported to improve depressed mood in obesity[197] as well as premenstrual depression,[135] bipolar depression,[200] seasonal affective disorder,[134] and bulimia nervosa.[201] Sibutramine's presumed mechanism of action (serotonin-norepinephrine reuptake inhibition[193,199]) is similar to that of the established serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant venlafaxine.[202] Sibutramine has displayed antidepressant properties in animal models of depression[203] and has improved depressed mood in patients with binge-eating disorder.[204] More recently, the novel anticonvulsants topiramate and zonisamide, which have both been associated with weight loss in epilepsy,[205,206] were each shown to be superior to placebo in inducing weight loss in obesity.[207,208] Although controlled trials of topiramate in acute bipolar I mania were negative,[209] the drug was as effective as bupropion in a single-blind controlled trial in bipolar depression.[210] Zonisamide has been reported to have therapeutic properties in bipolar mania in an open study.[211]

Studies of thymoleptics in obesity. Thymoleptics studied in placebo-controlled trials in obesity include several serotonin selective reuptake inhibitors (SSRIs) and bupropion. In particular, the SSRI fluoxetine was shown to have dose-related, modest, short-term (e.g., 6-week to 6-month) weight-loss effects in obese patients that were also associated with improvement in obesity-related medical risk factors such as hyperglycemia and hypercholesterolemia.[193,212–214] However, in long-term studies, all the weight was regained by 1 year. Bupropion was shown to be superior to placebo in inducing weight loss in obesity in 3 double-blind, controlled trials.[215–217] In one study, weight loss was maintained at 48 weeks.[217] Although venlafaxine is an SNRI like sibutramine, we found no studies of venlafaxine in the treatment of obesity. In studies of depression, however, venlafaxine was associated with anorexia and dose-related weight loss.[218,219] Venlafaxine was also reported to induce weight loss in a clinical study of obese women with binge-eating disorder, most of whom had a depressive disorder.[220]

In short, major depression and obesity are similar in their pharmacotherapy response in that each responds acutely to SSRIs, bupropion, and SNRIs. In addition, each condition shows maintenance of response to bupropion and SNRIs. However, they differ in their long-term response to SSRIs, with maintenance of response for 1 year

*References 7, 65, 66, 115, 122, 172, 191.

and longer established for major depression but not for obesity. Depression and obesity also appear to differ in their degree of response to these agents, with major depression responding more completely to SSRIs, bupropion, and SNRIs than does obesity. However, recent analyses of remission data from major depression trials comparing venlafaxine with SSRIs, which show greater remission rates with venlafaxine than SSRIs, suggest major depression may share with obesity a more complete response to SNRIs than to SSRIs.[221,222] Of course, the observations that obesity and major depression share some features of response to SSRIs, bupropion, and SNRIs stand in stark contrast to findings of antidepressant response with weight gain with tricyclics, mirtazapine, monoamine oxidase inhibitors, and even SSRIs (although controlled data have not consistently supported the latter observation).[17,34,35]

Although the mechanism(s) of the weight-loss effects of the SSRIs, bupropion, and venlafaxine are unknown, they may be similar to their hypothesized mechanisms in mood disorders. Thus, these agents have been hypothesized to decrease weight by selectively enhancing the function of anorexigenic neurotransmitters—serotonin for SSRIs[193]; norepinephrine, possibly with dopamine and serotonin, for bupropion[215,223,224]; and serotonin and norepinephrine for venlafaxine.[202] Zonisamide's weight-loss effects have similarly been hypothesized to be related, in part, to its dual serotonergic and dopaminergic effects.[207]

CONCLUSION

Although obesity and mood disorders are both increasingly serious public health problems, their relationship has been understudied and remains obscure. Nonetheless, based on the studies reviewed, several tentative conclusions can be made. First, the most methodologically sound clinical studies indicate that obesity, and the related conditions overweight and abdominal obesity, are common problems in persons seeking treatment for certain mood disorders (especially childhood-onset major depression[57] and bipolar disorder[18–21,63,64]), and conversely, mood disorders are common in persons of all ages seeking treatment for obesity (especially severe obesity).[22,25] Second, the more rigorous community studies suggest that (1) most persons in the community with obesity or overweight do not have a mood disorder[8,9,11,12,25,123]; but (2) certain mood disorders (especially major depressive disorder in young females[4] and major depressive disorder with atypical features in adults[45,59]) are associated with weight gain, overweight, and/or obesity; (3) obesity is associated with major depressive disorder in females[8,9,11,12,123] and possibly males,[9,11,12,123] whereas underweight is associated with major depressive disorder in males[4,8]; and (4) abdominal obesity may be associated with depressive symptoms in males and females.*

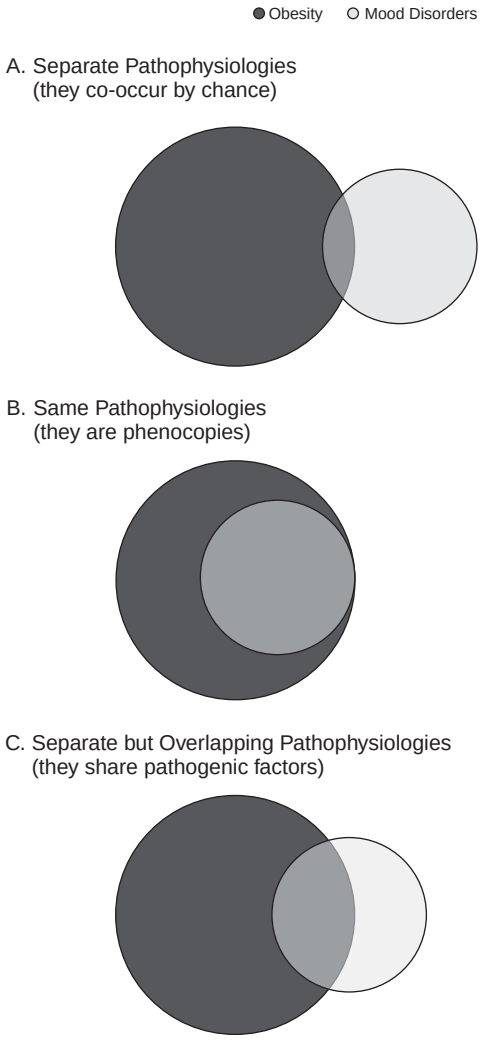
Third, obesity and mood disorders share other similarities. Phenomenologically, each may be characterized by overeating, physical inactivity, and weight gain,[124,125,132] and obesity is often accompanied by depressive symptoms.† Obesity and mood disorder are each associated with binge-eating behavior, as well as bulimia nervosa and binge-eating disorder.[139–153] General obesity, abdominal obesity, the metabolic syndrome, depressive disorders, and bipolar disorder are each associated with elevated morbidity and mortality from cardiovascular disease and type 2 diabetes.‡ Like mood disorders, extreme obesity has been characterized by elevated familial mood disorders.[171] Similar biological systems are deranged in both conditions. These include the HPAC axis,[172–176] central monoamine neurotransmitter systems,[176–179] leptin function,[180–182] immune function,[183,184] and glucose and lipid metabolism.[7,65,66,185–190] Regarding treatment response, both obesity and depression respond to medications that selectively enhance central serotonin, norepinephrine, and/or dopamine function.[193,199,202,222–225] Moreover, there are other similarities between obesity and mood disorders that were not addressed. Both conditions are associated with stigma and adverse childhood experiences,[225,226] and both may respond better to combinations of psychological and pharmacologic treatments than to either modality alone.[227,228]

Taken together, these data suggest that there may be a relationship between mood disorders and obesity beyond that due to iatrogenic factors and chance cooccurrence.[15] More specifically, at least among females, an important subtype of mood disorder might be depression (due to major depressive disorder or bipolar disorder) associated with weight gain and/or pathological overeating,[45,59] or alternatively, an important subtype of obesity might be that associated with a mood disorder and/or binge eating.[121,140] Moreover, mood symptoms may be an important feature of the metabolic syndrome,[114] or conversely, visceral fat deposition may be an important feature of certain mood syndromes.[7,65,66,191] Further attempts to subtype depression, therefore, should focus on why some individuals lose weight whereas others gain weight and explore relationships among weight and appetite, eating behavior, and motor activity, as well as energy balance and sleep architecture; neurotransmitter, peptide, endocrine, autonomic, and immune function; and glucose and lipid metabolism. Conversely, further attempts to subtype obesity should include evaluation of mood[45,129] and eating[48,52,145,146,148] pathology.

Indeed, 3 hypothetical models could explain the relationship between obesity and mood disorders (Figure 1). In the first, obesity and mood disorders are separate

*References 6, 105, 106, 113, 114, 116, 120, 122.
†References 3–6, 8, 23, 24, 70, 71, 81, 87, 98, 103, 105–107, 110, 113, 114, 116–120, 122.
‡References 14, 27–31, 43, 53, 55, 154–161, 165–170.

Figure 1. Three Hypothetical Models to Explain the Relationship Between Obesity and Mood Disorders



entities with distinct nonoverlapping pathophysiologies, which co-occur by chance but with significant frequency because they are both common conditions (Figure 1A). This model seems unlikely, however, in light of the clinical, epidemiologic, longitudinal, comorbidity, family history, biological, and treatment response similarities between obesity and mood disorders reviewed in this article.

In the second model, obesity and mood disorders are the same disorder with the same fundamental pathophysiology (Figure 1B). This model also seems unlikely in light of the epidemiological and treatment response differences between obesity and mood disorders reviewed. As discussed, most persons with obesity in the community do not have mood disorders, and melancholic major depression, especially in males, is associated with underweight. Also, obesity and major depression have a differential response to long-term treatment with SSRIs. Moreover, monogenetic forms of obesity have been identified, and obesity of presumed known etiology, including that comorbid with major depression,[229] has been reported to respond to specific treatment aimed at correcting the pathologic defect (e.g., leptin for congenital leptin deficiency[180] or metformin and spironolactone for polycystic ovary syndrome[229]).

In the third model, obesity and mood disorders are separate but related disorders with distinct but overlapping pathophysiologies (Figure 1C). In such a model, obesity and mood disorders, both heterogeneous, complex genetic illnesses, could share pathogenic factors, including heritable factors. Thus, there would be forms of obesity and mood disorder that were pathogenically related, as well as forms that were not related. Moreover, the degree of pathophysiologic overlap in individuals with both conditions could theoretically vary, depending on the nature or amount of inherited or acquired pathogenic material. This model would explain much of the clinical and epidemiologic data reviewed in this paper, as well as some of the phenomenologic, longitudinal, comorbidity, family history, and treatment response similarities and differences between obesity and mood disorders.

A pathogenic relationship between obesity and mood disorders would have implications for the treatment of both conditions. Current treatment guidelines for mood disorders[230,231] do not address the management of comorbid obesity and obesity-related conditions, while those for obesity[53,54] do not address the management of comorbid mood disorders. In light of the different weight-loss profiles of available thymoleptics, obese persons seeking treatment for mood disorders may need to be managed differently from those who are underweight. Similarly, in light of the potentially different thymoleptic profiles of antiobesity agents, obese persons with mood disorders seeking weight-loss treatment might need to be managed differently from those without mood disorders.[232] Thus, such patients may need their mood disorders treated before attempting diet and exercise programs.[53,233] Moreover, if mood disorders are "causative" of obesity in some cases, appropriate early treatment of the mood disorder may prevent the obesity.

Conversely, treatment with highly effective weight loss interventions may reduce comorbid depressive symptoms in particular obese populations, especially if the depression is secondary to the obesity.[13,204] Alternatively, since obesity is difficult to treat once it develops,[53] patients with both mood disorders and obesity may need thymoleptic agents in combination with weight-loss agents for optimal response (e.g., mood stabilizers and topiramate or zonisamide for bipolar disorder with obesity[232,234,235] or antidepressants with weight-neutral or weight-loss profiles [SSRIs, SNRIs, and bupropion] and topiramate for major depression and obesity[236,237]).

In short, a better understanding of the relationships among obesity; mood disorders; general medical illness; the beneficial and adverse effects of psychotropics on appetite, eating behavior, body weight, and metabolism; and the psychotropic effects of antiobesity agents should improve our ability to treat both obesity and mood disorders. Moreover, just as the weight and metabolic profiles of future psychotropics will need to be determined, so will the thymoleptic profiles of new antiobesity agents.

The above conclusions are admittedly preliminary, because they are based on relatively few systematically acquired data. There has been no large-scale psychiatric epidemiology study that has also assessed anthropometric measures. Conversely, no epidemiologic study of body weight has also assessed the full range of mood disorders with clinician-administered structured interviews. There have been no published controlled studies directly comparing a group of patients with obesity with a group of patients with mood disorders, or a group of persons with obesity with and without mood disorders. Surprisingly few studies of mood disorders have included body weight as a factor, whereas relatively few studies of obesity have included mood disorders as a factor. There are no controlled family history studies of psychopathology from non–treatment-seeking populations of obese probands. Also, there are few treatment studies in persons with both obesity and mood disorders. Moreover, there are important differences between obesity and mood disorders that may not be explained by a relationship between the two. For example, there appear to be important differences in the nature of HPAC axis dysregulation in both disorders. How much these differences represent different subtypes versus different disorders requires further study. In general, further research into the relationship between obesity and mood disorders is greatly needed.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac, and others), lithium (Lithobid, Eskalith, and others), metformin (Riomet, Glucophage, and others), methylphenidate (Methylin, Ritalin, and others), mirtazapine (Remeron and others), sibutramine (Meridia), spironolactone (Aldactone and others), topiramate (Topamax), venlafaxine (Effexor), zonisamide (Zonegran).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, fluoxetine, metformin, topiramate, venlafaxine, zonisamide, amphetamine, dexfenfluramine, and fenfluramine are not approved by the U.S. Food and Drug Administration for the treatment of obesity; metformin and spironolactone are not approved for the treatment of polycystic ovary syndrome; sibutramine and venlafaxine are not approved for the treatment of binge eating disorder; sibutramine, amphetamine, dexfenfluramine, and fenfluramine are not approved for the treatment of major depression; and topiramate and zonisamide are not approved for the treatment of bipolar disorder.

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