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SPECIAL ARTICLE

Physical health in affective disorders: a narrative review of the literature

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This article reviews the most common non-psychiatric comorbidities associated with affective disorders, examining the implications of their possible bidirectional link. A narrative review was conducted on the association among the three most common non-psychiatric diseases in major depressive disorder and bipolar disorder (obesity, metabolic syndrome, and cardiovascular diseases) in articles published from January 1994 to April 2020. The evidence suggests that obesity, metabolic syndrome, and cardiovascular diseases are highly prevalent in patients diagnosed with affective disorders. The presence of non-psychiatric comorbidities significantly worsens the therapeutic management and prognosis of affective disorders and vice versa. In many cases, these comorbidities may precede the onset of affective disorders, although in most cases they appear after it. The presence of these concurrent non-psychiatric diseases in an individual diagnosed with an affective disorder is associated with a more complex disease presentation and management. For professionals, the evidence unequivocally supports routine surveillance of comorbidities from a multidisciplinary approach.

Keywords: Bipolar disorder; major depressive disorder; comorbidities; obesity; metabolic syndrome; cardiovascular disease

Introduction

Severe mental disorders (SMD) globally contribute to 14% of the global burden of disease estimated by disability-adjusted life years.[1] Compared to the general population, patients with SMD suffer poorer health outcomes and high morbidity rates, as well as increased mortality.[1,2] Among all illnesses, major depressive disorder (MDD) is the second largest contributor to the chronic disease burden,[3] and bipolar disorder (BD) is the fifth leading psychiatric cause of lost working years, which represents a major public health concern. The relationship between SMD and increased mortality is often difficult to establish because most people with SMD do not die from their psychiatric illness, but other causes such as cardiovascular disease (CVD), other chronic non-psychiatric diseases, or suicide.[4,5]

Affective disorders, including MDD and BD, are among the psychiatric illnesses most frequently associated with mortality due to physical health. MDD bears a high mortality risk secondary to non-psychiatric diseases,[6] and represents an established risk factor for completed suicide.[7] Despite this, mortality rates in MDD are mainly due to non-psychiatric diseases such as cardiovascular-related pathologies (heart disease, hypertension, stroke, diabetes mellitus [DM], and obesity), Alzheimer's disease, or even cancer.[8] Many studies have hypothesized that increased mortality due to non-psychiatric diseases could be related to factors such as psychological reactions to illness, unhealthy behaviors, such as poor nutrition or drug use, pathophysiological abnormalities underlying MDD, and poor treatment adherence.[4,9-11] Similarly, BD has been associated with higher rates of premature mortality, which is not only attributable to disease-related causes (i.e., suicide), but also to multiple non-psychiatric diseases (i.e., cardiovascular, respiratory, cerebrovascular, and endocrine disorders or cancer), with a 50% higher mortality risk due to somatic diseases than the general population, as has been reported in meta-analytical data.[12-16]

Additionally, affective disorders with non-psychiatric comorbidities are associated with a more severe presentation of the psychiatric disease, greater treatment resistance, lower recovery rates, and worse course of illness.[12,17,18] On the one hand, multiple studies suggest that individuals with MDD or BD are at increased risk of developing non-psychiatric diseases such as DM, CVD, obesity, cancer, neurodegenerative diseases, etc.[19-21] On the other hand, people suffering from non-psychiatric diseases, especially more severe ones, seem to be at increased risk of

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developing affective disorders throughout life, thus suggesting a bidirectional link between non-psychiatric diseases and affective disorders.

This article aims to provide a focused narrative review of the currently available evidence of the main non-psychiatric comorbidities associated with affective disorders, underscoring their possible clinical, prognostic, and therapeutic implications. The non-psychiatric comorbidities reviewed in this study include three of the most prevalent and commonly found conditions in clinical practice: obesity, metabolic syndrome (MetS), and CVD.[8,12,19]

Methods

This qualitative overview focused on the current evidence about three of the main non-psychiatric diseases (obesity, MetS, and CVD) comorbid with affective disorders. To this end, a literature search was conducted in the PubMed and Cochrane databases on the association between CVD, MetS, and obesity in MDD and BD in articles published between January 1994 and April 2020. MeSH terms and free text terms for depression, bipolar disorder, metabolic syndrome, cardiovascular disease, and obesity were used. After screening and reviewing the titles and abstracts of the 1,084 total results, two of the authors (LC and GA) identified and retrieved the full texts of articles that seemed pertinent to highlight the current scientific evidence about obesity, MetS, and CVD related to MDD and BD. Additionally, the reference lists of the articles selected for inclusion were also searched for relevant reports. To provide an overview of the topic, we prioritized systematic reviews and meta-analyses summarizing the existing literature on the topic. The results of the included articles were synthesized narratively according to the included non-psychiatric comorbidities (CVD, MetS, and obesity). We provide a critical overview of the current scientific evidence about CVD, MetS, and obesity related to affective disorders, as well as perspectives on future directions.

Results

Obesity

Overweight and obesity are a public health priority. Epidemiological studies have estimated that about 50% of individuals from Organization for Economic Co-operation and Development countries are currently overweight and 18% are affected by mild-to-severe obesity.[22] Affective disorders and obesity frequently coexist.[23] Individuals with MDD have an increased probability of obesity (especially abdominal obesity) that is up to 50% greater than the general population. Obesity in MDD is characterized by atypical features, anxiety symptoms, and chronic course.[24,25] A meta-analysis of nine longitudinal studies including 7,196 subjects found that depression increased the odds of obesity at follow-up (odds ratio [OR] 1.58; 95% confidence interval [95%CI] 1.33-1.87).[26] Regarding BD, the prevalence of obesity is also increased, especially in patients with higher rates of depressive episodes.[27-29] Meta-analytical data show that the proportion of patients with abdominal obesity according to the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) or ATP-III-A criteria was 48.7% (95%CI 46.2-51.2), and it was 61% (95%CI 51.9-63.4) according to International Diabetes Federation criteria, especially in patients with higher rates of depressive episodes.[29]

BD and MDD are affective disorders that impair appetite, energy, and motivation. Depressive symptoms have also been linked to increased tobacco and alcohol use, and poor treatment compliance for non-psychiatric diseases, as well as unhealthier lifestyles.[18,30,31] These factors can lead to increased vulnerability to obesity, typically including increased abdominal circumference.[32-34]

Affective disorders share pathophysiological pathways with obesity, such as increased cortisol levels and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which seems to predispose people to increased central adipose tissue deposition.[33] A meta-analysis of 17 community-based studies including a total of 204,507 participants found that obese people were more likely to have depressive symptoms than those without obesity (OR 1.18; 95%CI 1.01-1.37).[35] In addition, meta-analytical data from eight longitudinal studies including 55,387 subjects found evidence that overweight and obesity increased the odds of subsequent depression, with ORs of 1.27 (95%CI 1.07-1.51) and 1.55 (95%CI 1.22-1.98), respectively,[26] which suggests a bidirectional link between obesity and affective disorders. Furthermore, sleep disturbances – common in BD and MDD – also increase the risk of obesity due to: 1) behavioral causes (insomnia increases the risk of nocturnal binges); 2) neurobiological reasons – decreasing leptin levels (leading to decreased satiety),which leads to increased ghrelin levels (also known as the hunger hormone) or decreased adiponectin (a hormone related to glycidic and lipid homeostasis); and 3) induction of inflammatory cytokines.[33,36,37] In fact, obesity, BD, and MDD have been considered by some authors to share a state of low-grade chronic inflammation.[12,32,33]

A mismatch in neurotransmission systems may also be implicated in the bidirectional association between obesity and affective disorders, since obesity can be a consequence of binge eating disorder, in which dopaminergic dysregulation is implicated. Reward pathways are mediated by the dopaminergic system, and its manipulation may affect the craving for substances, including food. Both obesity and affective disorders share dysregulation of the dopaminergic system (i.e., low density of D_2 receptors at the striatal level). Evidence points to overlapping neuronal circuits between obesity and affective disorders, such that people with BD and comorbid obesity seem to be less vulnerable to drug use disorders, whereas people with BD and comorbid drug use disorders seem less likely to be obese.[33,38]

Another important factor that contributes to higher rates of obesity in affective disorders is iatrogenic weight gain due to common affective disorder treatments, including second-generation antipsychotics, mood stabilizers, and antidepressants. However, not all treatments have the same potential to induce weight gain.[33,39,40] For instance, atypical antipsychotics, particularly olanzapine and clozapine, induce severe weight gain due to 5HT2c, antihistaminergic, and antimuscarinic blockade.[39]

Finally, comorbid obesity in both MDD and BD is associated with greater severity, poorer outcomes, poorer treatment response, higher suicide rates, higher risk of recurrence, and poorer global functioning and perceived quality of life. These associations persist after adjusting for confounders such as gender, race, marital status, any current anxiety disorder, binge eating, and treatment with medications associated with weight gain.[32,38,41]

Metabolic syndrome

MetS is a clinical construct that defines a preclinical state of CVD and DM. Current criteria for MetS include central obesity, hyperglycemia, low high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, and arterial hypertension (Figure 1).[42,43]

Bipolar disorder

A meta-analysis of 37 studies including 6,983 patients with BD showed that the prevalence rate of MetS was 37.3% (95%CI 36.1-39.0), being MetS almost twice as common in BD as in the general population (OR 1.98; 95%CI 1.74-2.25).[44] There are multiple explanations for this association, including reduced access to medical care, harmful lifestyles, neurobiological abnormalities, and common genetic susceptibilities, as well as the side effects of psychotropic medications.[17,45,46] Neurobiologically, MetS and BD share many pathophysiologic alterations, such as multiple genetic variants related to the signaling pathways of corticotropin-releasing hormone, serotonin and dopamine receptors, circadian rhythm, and leptin, as has been described in meta-analyses of genome-wide association studies and candidate gene studies.[47] In addition, MetS and BD share pathophysiologic alterations in homeostatic systems, such as the HPA axis (particularly hypercortisolemia),[12,48] and abnormal inflammatory responses, as well as the gut microbiota system, which plays a critical role in metabolism, immunity, and even neurobiology.[12,49]

The role of psychotropic medication in this association has been extensively studied. Patients with BD have shown an increased risk of MetS when treated with antipsychotics, especially clozapine or olanzapine.[29,39,40,50] Psychotropic medication can lead to increased appetite and weight gain, as well as to MetS[51] through metabolic dysregulation due to increased oxidative stress, which affects glucose metabolism and increases lipogenesis.[52-54] Mood stabilizers, such as lithium or valproic acid, have also been associated with increased MetS, especially when used in combination with antipsychotics.[55] Nevertheless, an increased risk of MetS has also been found in drug-naïve BD patients. Thus, it is not associated with psychotropic drugs alone.[44]

Finally, some of the clinical features of BD include hyperphagia, hypersomnia, and reduced physical activity,[37] which may lead to MetS, especially in depressive episodes.[56-58]

Major depressive disorder

MetS is present in approximately 30.5% of patients with MDD.[6,59] Compared with healthy controls, meta-analytical data suggest that patients with MDD had a significantly increased risk of MetS (OR 1.54; 95%CI 1.21-1.97).[59] Regarding individual MetS criteria, further meta-analytical data suggest that about 40% of individuals with MDD had abdominal obesity or hypertension, about 30% had abnormal HDL-C or triglycerides, and 20% had clinically significant pre-diabetes, and, compared with healthy controls, individuals with MDD had significantly increased fasting hyperglycemia (OR 1.33; 95%CI 1.03-1.73), hypertension (OR 1.42; 95%CI 1.09-1.86), and hypertriglyceridemia (OR 1.17, 95%CI 1.04-1.30).[59,60]

Such results are mainly due to the association between MDD and obesity-related MetS components (abdominal obesity, low HDL, and hypertriglyceridemia), while associations with hyperglycemia and hypertension are less frequent.[6] Moreover, pathophysiological features, such as autonomic nervous system activity dysfunction, HPA axis dysregulation, immunoinflammatory abnormalities, vascular endothelial dysfunction, and gut microbe dysbiosis are common to both disorders, and common genetic and epigenetic links are shared.[6,44,61]

In addition, reduced access to health care, poor lifestyle conditions, side effects of psychotropic medications,

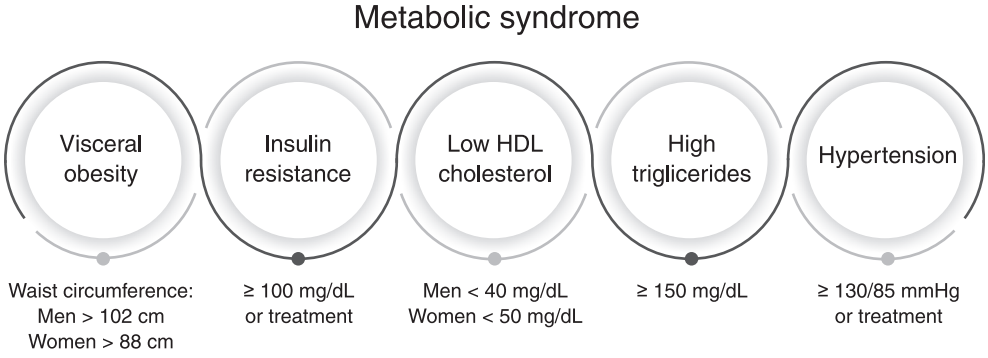

Figure 1 Working criteria for the metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (ATP-III).[43] Visceral obesity is measured by waist circumference in cm. Due to the difficulty of measuring insulin resistance in clinical settings, the ATP III criteria include fasting plasma glucose, treatment with insulin or hypoglycemic medication, low HDL, hypertension, or treatment with antihypertensive medication. 3/5 criteria required.

and modifiable behavioral risk factors, such as smoking and physical inactivity, may also contribute to a higher prevalence of MetS in MDD.[6,46] Among treatments, tricyclic antidepressants and antipsychotics have been associated with a greater risk of MetS in MDD.[62]

From a clinical point of view, certain MDD subtypes and symptom profiles, such as atypical depression, are more closely associated with MetS.[6]One explanation for this association could be that atypical depression usually presents with hyperphagia and hypersomnia,[37] as well as with significantly higher levels of inflammatory markers, body mass index, waist circumference, triglycerides, and lower HDL cholesterol than melancholic depression.[44]

MetS can also contribute to a more complex presentation and worse clinical outcomes in MDD by leading to a worse course of illness, including more depressive episodes and suicide attempts and less responsiveness to treatment.[6,17] Therefore, a bidirectional relationship between MetS and MDD is suggested.[17,63]

Cardiovascular diseases

Bipolar disorder

The high rates of morbidity and mortality in BD are closely connected to CVD.[18] The burden of CVD is a major contributor to the fact that BD patients die 10-15 years earlier than the general population.[64,65] Some cohorts have described three-fold higher mortality due to cerebrovascular disease and two-fold higher mortality due to myocardial infarction and coronary heart disease in BD compared to the general population.[66] Specifically, according to meta-analytical data, BD patients have a greater risk of mortality due to circulatory-related problems such as heart attacks (OR 1.73; n=153,948; 95%CI 1.54-1.94) than healthy non-psychiatric populations.[13]

Individuals with BD may have poorer diets, be less physically active, and consume more tobacco and other toxic substances, even compared to other SMD.[46,62,67] Furthermore, other CVD risk factors, such as obesity, arterial hypertension, or DM, are more prevalent in BD, which could explain the higher risk of developing CVD.[67]

Another possible explanation for higher CVD comorbidity and mortality can be attributed to psychopharmacological treatment. Mood stabilizers, including lithium and valproic acid, and second-generation antipsychotics may induce weight gain, as well as alterations in glucose metabolism.[39,40] In addition, second-generation antipsychotics are also associated with dyslipidemia.[68] Unfortunately, these patients may receive less monitoring and treatment than the general population, in spite of the great need for it.[67]

Major depressive disorder

MDD is associated with an 80-90% increased risk of developing CVD and peripheral atherosclerosis, according to a meta-analysis that integrated longitudinal evidence from 21 studies involving over 120,000 subjects.[69-73] Another meta-analysis of 30 prospective cohort studies with a total of 893,850 subjects suggests that MDD is associated with an 30% higher risk of coronary heart disease and myocardial infarction with relative risks of 1.30 (95%CI, 1.22-.40) and 1.30 (95%CI ?1.18-1.44), respectively.[60] In addition, MDD has been associated with increased CVD mortality in patients already suffering from CVD.[74] Therefore, MDD appears not only to be associated with CVD onset, but also with a worse clinical course and prognosis for CVD pathology. Conversely, CVD may increase the risk of developing depressive symptoms and MDD, which suggests a bidirectional interaction between MDD and CVD.[69]

The underlying mechanisms that lead to increased CVD in individuals with MDD probably involve unhealthy lifestyles, reinforcing a vicious cycle in which MDD and CVD interact.[31,46,60,69] However, a bidirectional link between CVD and MDD has not yet been elucidated.[60,69]

Discussion

The analyzed evidence indicates that people with affective disorders seem to have higher rates of non-psychiatric comorbidities than the general population and vice versa. However, the association rates differ between studies, so future research is needed to quantify this association. Moreover, individuals with affective disorders and non-psychiatric comorbidities, including obesity, MetS, and CVD, usually have a more severe presentation of the affective disorder, with a worse evolution and prognosis, including earlier age of onset, more severe symptoms, increased risk of suicide, poor recovery, decreased response to pharmacological and psychosocial treatment, poorer quality of life, as well as less probability of functional recovery and lower recovery rates, including direct or indirect medical, social and economic repercussions.[9,75-77] Several factors may contribute to this association, including the fact that people with affective disorders usually have less access to public and private health care systems than the general population, tend to have unhealthier lifestyle habits, including poor-quality diets, physical inactivity, a higher prevalence of drug use, including tobacco and alcohol; psychopharmacological treatment, such as antipsychotics, mood stabilizers, and antidepressants, some of which are associated with increased appetite and weight gain; and have symptomatic presentations in depressive or (hypo) manic episodes, such as increased appetite, insomnia, hypersomnia, apathy, and decreased activity, which facilitate weight gain, MetS and, secondarily CVD.[31,46,62,78] The differences between BD and MDD in obesity, MetS, and CVD are shown in Table 1.

Furthermore, all international guidelines on affective disorders[79-83] highlight the need to consider non-psychiatric associated comorbidities in affective disorders and call for early detection and better screening strategies. Some guidelines even provide specific recommendations on the clinical management of non-psychiatric comorbidities.[84-88] Most recommendations suggest that psychoeducation and family participation in the care process play a key role, as well as the need for integrated and coordinated treatment by multidisciplinary teams, including primary healthcare physicians.[89,90] Better management of

Table 1 Comparison between medical comorbidities and affective disorders

Medical comorbidities	BD	MDD
Obesity		
Prevalence	48.7% (95%CI 46.2-51.2)*	-
Measures of association		
Affective disorders in obesity	-	Depression increased the odds of obesity at follow-up (OR 1.58; 95%CI 1.33-1.87)
Obesity in affective disorders	-	Obesity increased the odds of subsequent depression (OR 1.55; 95%CI 1.22-1.98)
Pathophysiology	Dysregulation of the HPA axis Increased cortisol levels Decreased leptin levels Increased ghrelin levels Decreased adiponectin levels Induction of inflammatory cytokines Dopaminergic dysregulation Gut microbe dysbiosis	
Lifestyle	Increased use of tobacco, alcohol, and other substances Poor treatment compliance Physical inactivity Reduced physical activity Poor diet Less access to medical care	
Treatment	Common BD treatments related to obesity: First and second-generation antipsychotics Mood stabilizers Lithium Valproic acid	Common MDD treatments related to obesity: Tricyclic antidepressants Monoamine oxidase inhibitors Mirtazapine Paroxetine
Clinical factors	Depressive episodes Sleep disturbances Hypersomnia Binge eating	Atypical depression Sleep disturbances Binge eating
MetS		
Prevalence	37.3% (95%CI 36.1-39.0)	30.5% (95%CI 26.3-35.1)
Measures of association		
Affective disorders in MetS	BD increased the odds of MetS (OR 1.98; 95%CI 1.74-2.25)	MDD increased the odds of MetS (OR 1.54; 95% CI 1.21-1.97)
MetS in affective disorders	-	-
Pathophysiology	Genetic susceptibilities Dysregulation of the HPA axis Increased cortisol levels Decreased leptin levels Increased ghrelin levels Decreased adiponectin levels Induction of inflammatory cytokines Dopaminergic dysregulation Gut microbe dysbiosis Vascular endothelial dysfunction	
Lifestyle	Increased use of tobacco, alcohol, and other substances Poor treatment compliance Physical inactivity Reduced physical activity Poor diet Less access to medical care	
Treatment	Common BD treatments related to MetS: First and second-generation antipsychotics Mood stabilizers Lithium Valproic acid	Common MDD treatments related to Mets: Tricyclic antidepressants Monoamine oxidase inhibitors Mirtazapine Paroxetine

Continued on next page

Table 1 (*continued*)

Medical comorbidities	BD	MDD
Clinical factors	Depressive episodes Sleep disturbances Binge eating	Atypical depression Sleep disturbances Binge eating
CVD		
Prevalence	-	-
Measures of association		
Affective disorders in MetS	BD increased risk for mortality due to heart attacks with (OR 1.73; 95%CI 1.54-1.94)	MDD increased risk for mortality due to heart attacks (RR 1.30; 95%CI 1.18-1.44)
MetS in affective disorders	-	-
Pathophysiology	Genetic susceptibilities Dysregulation of the HPA axis Increased cortisol levels Induction of inflammatory cytokines Gut microbe dysbiosis Vascular endothelial dysfunction	
Lifestyle	Increased use of tobacco, alcohol and other substances Poor treatment compliance Physical inactivity Reduced physical activity Poor diet Reduced access to medical care	
Treatment	Common BD treatments related to MetS: First and second-generation antipsychotics Mood stabilizers Lithium Valproic acid	Common MDD treatments related to Mets: Tricyclic antidepressants Monoamine oxidase inhibitors
Clinical factors	Sleep disturbances Higher prevalence of cardiovascular risk factors as metabolic disturbances or hypertension	

95%CI = 95% confidence interval; BD = bipolar disorder; CVD = cardiovascular diseases; HPA = hypothalamic-pituitary-adrenal axis; MDD = major depressive disorder; MetS = metabolic syndrome; OR = odds ratio; RR = relative risk.
* According to National Cholesterol Education Program Adult Treatment Panel III (ATP-III) or ATP-III-A criteria.

both non-psychiatric and affective disorders would imply better outcomes, course of illness, functioning, and quality of life in both non-psychiatric and affective disorders.

Finally, although non-psychiatric comorbidities may precede the onset of affective disorders in some cases, they usually emerge after diagnosis. The studies reviewed herein indicate that patients with an affective disorder have a higher risk of developing obesity, MetS, or CVD and that patients with non-psychiatric comorbidities have an increased risk of developing mood disorders. The nature of this interaction encompasses from the clinical aforementioned factors to the shared neurobiological pathophysiology of both disorders, including alterations in the HPA axis, the serotonin and dopaminergic systems, circadian rhythm, leptin-ghrelin and related hunger-regulatory hormones, immuno-inflammatory abnormalities, autonomic nervous system dysfunction, vascular endothelial dysfunction, and gut microbe dysbiosis, as well as common genetic and epigenetic variants (Figure 2). All evidence suggests that common pathophysiological processes underlie affective disorders and these non-psychiatric illnesses, indicating a bidirectional link between affective disorders and obesity, MetS, and CVD.

Therefore, close monitoring of patients diagnosed with affective disorders and medical comorbidities is essential to prevent poor outcomes and treatment resistance. A multidisciplinary approach is recommended in which psychiatrists, psychologists, mental health nurses, and general practitioners collaborate to improve patient lifestyles and discuss the best pharmacological and psychological treatment for each patient.

The following study limitations should be considered. First, considerable methodological heterogeneity was found across the included studies. The evidence about the interaction between affective disorders and obesity, MetS, and CVD contains data from different populations and countries with differing cultural and medical backgrounds. Thus, quantifications of prevalence and association measures varied widely between some studies. The meta-analytical data included in this review come from studies with substantial variations in quality: limited sample sizes, reliance on cross-sectional retrospective studies, and insufficient pretreatment information on obesity, MetS, or CVD in the enrolled participants. Second, in our review of the current body of evidence (especially meta-analytical data), we found no studies that reported a negative association between affective disorders and comorbid obesity, MetS, or CVD compared with the general population. Third, our findings were based on cross-sectional, rather than randomized or longitudinal data. Thus, the directionality of potential mediators and

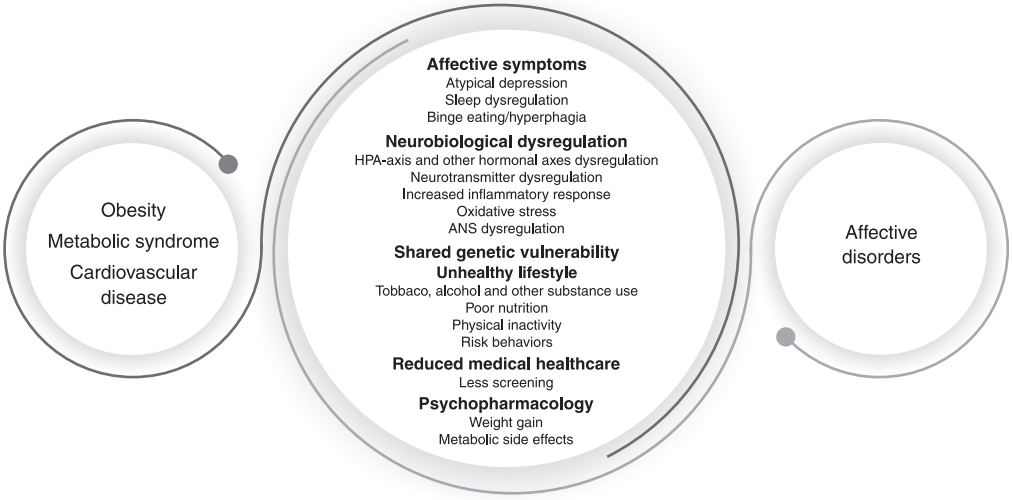

Figure 2 Possible mechanisms explaining the bidirectional relationship between affective disorders and obesity, metabolic syndrome, and cardiovascular disease. ANS = autonomic nervous system; HPA = hypothalamic-pituitary-adrenal axis.

moderators, such as lifestyle habits, treatments, and drug use, and the evaluated medical comorbidities could not be deduced with certainty.

We believe that our work provides a comprehensive and clinically-focused review of the existing knowledge regarding the interrelation between most common comorbidities and affective disorders. Several gaps in the current literature have been highlighted and we offer some insight on the common therapeutic strategies for tackling both affective disorders and physical comorbidities as a whole, as well as new lines of research to improve current knowledge about their bidirectional link.

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Disclosure

LC reports no conflicts of interest. GA has received continuing medical education (CME)-related honoraria or consulting fees from Janssen-Cilag, Lundbeck and Angelini. EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Galenica, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sage, Sanofi-Aventis, Servier, Shire, Sunovion, and Takeda. IG has received grants and served as consultant, advisor or CME speaker for the following entities: Angelini, AstraZeneca, Casen Recordati, Ferrer, Janssen Cilag, Lundbeck, Lundbeck-Otsuka, and SEI Healthcare.

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