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# Premorbid obesity and metabolic disturbances as promising clinical targets for the prevention and early screening of bipolar disorder

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ABSTRACT

Recent evidence shows an important relationship between metabolic disturbances and bipolar disorder (BD). However, it is still unclear whether such metabolic disturbances are only a consequence or to some extent the precipitating factors for health problems and maladaptive behaviors observed in BD. Because both metabolic disturbances and BD are medical conditions sharing common alterations in multiple biomarkers, it is plausible to hypothesize that metabolic disturbances may be considered to some extent as a major vulnerability factor in the latent phase of BD for some young adults. In line with this hypothesis, obesity may be regarded as a major driving force for prevalent cardio-metabolic disorders encountered within the early stages of BD. Likewise, premorbid metabolic disturbances as a whole may be considered as a potential source for vulnerability to develop BD. In addition, a synergistic relationship between obesity and metabolic disturbances associated with a premorbid disruption of biological rhythms may also lead to BD. Therefore, we postulate that metabolic disturbances may serve as a specific marker of premorbid illness activity in some people at risk for BD. Future prospective studies should focus on validating metabolic disturbances as vulnerability factors within the staging model of BD.


## Introduction

Bipolar disorder (BD) is a disabling mental illness with a significant mortality risk due to suicidality, metabolic disturbances, and unhealthy lifestyle habits such as smoking, substance/alcohol abuse, lack of exercise, and sedentary behavior [1]. As a consequence, several stress-related medical comorbidities including cardiovascular disorders (CVD), Type 2 Diabetes (T2D), obesity, migraine, and chronic pain among others tend to be over-represented in patients with BD [2].

The risk of developing CVD in BD is 5-times higher than that reported in the general population and 2-times that reported in major depressive disorder (MDD) patients [4]. Moreover, there is evidence showing that the comorbidity between BD and T2D is associated with increased risk of recurrences, frequent hospitalizations, greater severity of illness, suicidality and a poorer overall response to mood stabilizers [5–8]. A history of lifetime manic spectrum episodes in early and middle adulthood has also been related with an increased risk of all-cause mortality including, but not limited to, CVD and T2D [9]. Based on these clinical findings, metabolic disturbances could be considered as significant medical risk factors for BD and other coexisting medical comorbidities. Indeed, metabolic disturbances driven by obesity have been shown to accelerate disease activity, staging and progression in BD [13]. Furthermore, the loss of functional capacity cognitive impairment, and risk of developing rapid cycling bipolar disorder (RC-BD) appear to be enhanced by the presence of metabolic disturbances [1,13]. Nevertheless, it is still unclear whether metabolic disturbances are the consequences or the leading factors of some of the health problems and maladaptive behaviors observed in BD [10–12].

In this review we highlight metabolic disturbances as potential predisposing factors for the development of BD which may also

*Abbreviations:* CLOCK, Circadian Locomotor Output Cycle Kaput; BDNF, Brain Derived Neurotrophic Factor; BD, bipolar disorder; MetS, metabolic syndrome.

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enhance the occurrence of multiple medical conditions over the course of bipolar illness [6,14,15].

## Hypotheses connecting metabolic disturbances with bipolar disorder

### *Obesity as a major driving force for metabolic disturbances in bipolar disorder*

An initial hypothesis is to consider that obesity is the major driving risk factor for a number of prevalent medical disorders associated with metabolic disturbances encountered in BD such as Type 2 Diabetes (T2D), hypertension, atherosclerosis, low high-density lipoprotein cholesterol levels, and hypertriglyceridemia [16–18]. The accumulative presentation of three or more of these obesity-related medical conditions constitutes what is referred to as the metabolic syndrome (MetS) [17,18]. It has been reported that metabolically healthy overweight (Body Mass Index – BMI 25–29.9) and obese (BMI > 30) individuals not suffering from BD showed an increased risk for CVD, CVD-related death, and all-cause death compared with normal-weight metabolically abnormal individuals [19]. Not surprisingly, metabolically abnormal obese individuals had the highest risk for CVD and mortality. Therefore, obesity may partly explain the CVD risk documented in early to mid-stages of the course of illness neuroprogression of BD [3,4,81,95]. Although it is well-established that in BD the association risk between metabolic disturbances and CVD is relatively high and related to significant medical burden, the impact of obesity on the risk of developing these conditions, regardless of its nature and its role in the causal chain of events, may be of crucial significance [3,4].

### *Premorbid metabolic disturbances as vulnerability risk factors for bipolar disorder*

At the beginning of the 20th century, Ernst Kretschmer (1888–1964) alluded to the fact that some physical properties of the body structure were linked to character and psychiatric illness [20]. In fact, Kretschmer was the first researcher in modern psychiatry to describe a relationship between premorbid physical or psychological characteristics linked to a possible etiology of mental disorders. He established the well-known trifold typology of the "leptosome," "athletic," and "pyknic" habitus; the latest typology referring to obesity and the risk of suffering from manic-depressive illness [20,21]. According to this typology, obesity may be considered as being the premorbid condition for the development of not only medical disorders associated with bipolar illness as stated before, but also a major vulnerability factor in populations at risk for bipolarity.

Research findings have shown that a high BMI (>25) is associated with suffering from metabolic disturbances and chronic obesity [19,27]. Additionally, overweight and obesity are considered risk factors for the development of neurodegenerative diseases such as Alzheimer Disease (AD) and are involved in the pathophysiological processes of other mental illnesses including mood disorders [6,17,22]. Over the past two decades, numerous studies have shown that obesity is associated with increased inflammation, oxidative stress, HPA abnormalities, neurotransmitter imbalances, mitochondrial dysfunction and a faster functional and cognitive decline in major psychiatric disorders [7]. Accordingly, obesity is linked to a 25% increase in the association risk of suffering from any mood disorders and about half of this increase is associated with the development of BD [6,28]. Moreover, the National Comorbidity Survey (NCS) reported a 12-month and lifetime higher prevalence of BD in obese individuals (BMI > 30) when compared with overweight subjects (BMI 25–29.9) and healthy controls (BMI < 25) [28].

Obese patients suffering from binge eating disorders (BED) have a sixfold increased risk of suffering from BD [6]. Likewise, it has been shown that obesity and BD exhibit common phenomenological spectrums such as "emotional eating", hyperphagia, diminished physical activity, fluctuations in energy levels, fatigue, dysphoria, psychomotor retardation, and disrupted sleep patterns [14,15]. In a recent epidemiological survey focusing on obesity in BD, all the medical symptoms shared by obesity and bipolar spectrum disorders were found to be predictive of medical conditions associated with metabolic disturbances such as hypertension, diabetes, hyperlipidemia, myocardial infarction (MI) and arthritis [15]. These findings suggest that premorbid obesity-driven metabolic disturbances could be considered as primary vulnerability factors for some patients with BD. Thus, metabolic disturbances may be regarded as modulating factors in the expression of a more complex and severe endophenotype of bipolar illness.

### *Synergistic relationship between obesity and metabolic disturbances associated with a premorbid disruption of biological rhythms leading to bipolar disorder*

Obesity and persistent metabolic disturbances may be involved in a synergistic relationship associated with the disruption of the biological rhythms frequently encountered early on in patients with BD [7,23–26]. While previous studies argue that the disruption of biological rhythms may induce weight gain and metabolic disturbances in BD, it is also well-established that sleep disturbances are implicated in obesity, poor diet and insufficient or inadequate exercising related with inter-episode dysfunction, adverse health outcomes and subsequent relapses and recurrences in BD [23,24]. Consistent with these findings, some authors have postulated that evening chronotype BD patients have a higher percentage of total body fat composition that may lead to metabolic disturbances [25]. Furthermore, it has been demonstrated that sleep deprivation in BD may be related to altered expression of genes involved in regulating metabolic processes, response to stress and inflammation, circadian sleep/wake patterns, reduced mitochondrial activity in the hypothalamus, cell proliferation and signaling in various pathways of interest for both BD and metabolic disturbances [26]. Last but not least, circadian rhythm instability can be induced by changes associated with hypothalamic–pituitary–adrenal (HPA) axis dysfunction, which is shared by both obesity and BD [7]. As far as we are aware, multiple factors associated with obesity and metabolic disturbances appear to be related with the dysfunctional circadian patterns of sleep/wake cycles frequently encountered early on in BD. However, it is still unclear, if this relationship is the primary vulnerability factor in metabolically disturbed patients at risk for BD.

To summarize, the clinical relationship between metabolic disturbances and BD is a growing area of interest in mood disorders research that merits further investigation. Thus far specific data focusing on metabolic disturbances (including obesity) as possible vulnerability factors for populations of young adults at risk of developing BD continues to be scarce. Nevertheless, exploring shared genetic vulnerability, inflammatory and oxidative stress processes, neuroimaging changes and neurocognitive impairment underlying metabolic disturbances in people at risk of developing BD would assist in the validation of the proposed hypothetical frameworks. It is likely that a multifactorial inclusive assessment model accounting for a broad spectrum of biological markers shared by premorbid metabolic disturbances and BD will increase the sensitivity and specificity of the model in predicting early illness activity and progression in individuals at risk.