

# Cardiometabolic Comorbidity in Bipolar Disorder

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Bipolar disorder is a common mental disorder which is present in approximately 2% of the general population (1). In addition to significant psychiatric morbidity, bipolar disorder is also associated with a range of poor physical health outcomes and excess mortality (2-4).

Recently there has been renewed interest in the association between cardiometabolic illness and major mental illness. Traditionally, the focus has been on depression and schizophrenia (5) but more recent work has highlighted this as a major issue for bipolar disorder (6).

In this article we outline the main problems individuals with bipolar disorder face with regards to cardiometabolic disease and provide a synopsis of possible mechanisms. We also make suggestions for further research and clinical practice aimed at reducing cardiometabolic morbidity and mortality in bipolar disorder.

## **Bipolar Disorder and Cardiovascular Disease**

It has been noted for a long time that individuals with bipolar disorder have disproportionately high levels of cardiovascular disease and premature mortality. More than thirty years ago, Tsuang et al. (7) reported in their seminal "Iowa 500" Study that bipolar disorder was associated with a significant excess of mortality in women, with a standardised mortality rate (SMR) of 1.63.

In their 1994 paper on mortality in affective disorder, Sharma et al. (8) prospectively followed up 472 individuals with bipolar disorder over 17 years. In what was one of the first prospective cohort studies examining cardiometabolic health in bipolar disorder, 42.1% of deaths in the study group were due to cardiovascular disease compared to 15.7% attributable to suicide and 33.3% to respiratory disease. Furthermore, those who died due to poor physical health were more likely to be unmarried, with greater frequency and duration of admissions, and were less likely to receive lithium therapy (8).

More recently, in a Swedish population study of excess mortality in bipolar and unipolar mood disorder, Osby et al. (9) reported 2129 excess deaths in a sample of 15,386 individuals with bipolar disorder. 700 of these deaths were due to vascular disease. Overall, vascular disease (cardiovascular and cerebrovascular) is now thought to be the leading cause of excess mortality in bipolar disorder (6-9).

There is evidence that bipolar disorder is associated with numerous different cardiovascular diseases (10,11). Hypertension is present in around one third of patients and hyperlipidaemia in around 10% (10). Despite strong epidemiological evidence that bipolar disorder and cardiovascular disease are linked, the mechanisms underlying this are poorly understood. There are known to be direct physiological consequences of mood disorder on cardiovascular risk, such as decreased heart

rate variability, increased platelet adhesiveness and higher levels of inflammatory risk markers (C-reactive protein and interleukin-6) (12,13). Hypothalamic-pituitary-adrenocortical (HPA) axis dysregulation is likely to play a role in this area. Elevated serum cortisol levels promote the development of atherosclerosis, are linked to hypertension and are thought to cause vascular endothelial damage (14). Sympathoadrenal abnormalities identified in depression are likely also to play an important role in the relationship between bipolar disorder and cardiovascular disease (14).

Inflammation and hypercoagulability are also thought to be relevant in the link between mood disorder and cardiovascular disease. Patients with depression have been found to have elevated levels of inflammatory markers which are associated with accelerated atherosclerosis and poor cardiovascular outcomes (14).

### **Bipolar Disorder and Diabetes**

Individuals with bipolar disorder are known to be at increased risk of developing type II diabetes mellitus. Although the link between bipolar disorder and type II diabetes has been known for some time (10,15,16), relatively few population-based studies of prevalence and correlates of diabetes in bipolar disorder have been conducted. Prevalence rates of diabetes in the bipolar population are estimated to be between 10 and 26% (10,17).

Moreover, there is evidence that a significant proportion of diabetes is undetected, and this may be a particular problem in individuals with major mental illness (18,19). True rates of diabetes mellitus in bipolar disorder may be somewhat higher than previously thought.

Patients with comorbid diabetes and bipolar disorder have additional challenges in terms of diabetic control and risk of complications. Mood symptoms can adversely affect self management in a variety of disorders (12). In their 2000 metanalysis, DiMatteo et al. (20) found that individuals with depression were three times more likely to be non-compliant with medical recommendations compared to those without

depression. Similarly, Ciechanowski et al. (21) found that the severity of depressive symptoms was associated with non-adherence to oral hypoglycaemic agents in type II diabetics and a greater likelihood of contact with physical health services. Although there is relatively little information available on diabetic morbidity and mortality in bipolar disorder, it seems likely that, as with depression, there will be an association with poor diabetic control and possibly higher rates of diabetic complications.

There are several possible mechanisms, which might link bipolar disorder and type II diabetes. These include lifestyle factors, the effects of psychotropic medications such as mood stabilisers and antipsychotics, HPA axis dysregulation, and genetic or signal transduction dysfunctions (22,23).

### **Bipolar Disorder and Obesity**

Recent studies indicate that approximately one third of patients with bipolar disorder are obese (24). Obesity is associated with poorer psychiatric outcomes in bipolar disorder (25), including increased rates of relapse and more difficult-to-treat mood episodes. Furthermore, severity of mood disorder episodes in bipolar disorder have been positively correlated with degree of weight gain (25).

Although lifestyle factors are known to be important, there is also evidence that individuals with bipolar disorder have higher levels of abdominal and visceral fat and reduced rates of fat oxidation compared to controls matched for obesity, age, gender and ethnicity. These changes, which are likely to be independent of lifestyle, may predispose to obesity and associated cardiometabolic disease (26,27). Furthermore, disturbances in the sleep cycle circadian rhythm (28), and in particular the presence of an evening circadian chronotype, may account for approximately 20% of excess obesity in bipolar disorder (29). Self-reported poor sleep quality and insomnia, which are common in bipolar disorder, have also been associated with increased BMI, waist circumference, body fat percentage and measures of insulin resistance (29-31).

## **Bipolar Disorder and Cardiometabolic Risk Factors**

Despite evidence that there is shared genetic vulnerability between bipolar disorder and cardiometabolic disease, the role of lifestyle factors is likely to be very important. The cumulative effects of high rates of smoking and alcohol use, as well as physical inactivity, play a significant role (12,32).

Smoking is substantially more common in people with bipolar disorder, perhaps more so than in other serious mental illnesses (33). Rates of current smoking in bipolar disorder are estimated to be as high as 68.8% and rates of a lifetime history of smoking at 82.5%, considerably higher than rates of smoking in schizophrenia (33). Rates of quitting smoking have also been reported to be lower than for other major mental illnesses (33).

The lifetime prevalence of alcohol use disorders in bipolar disorder is approximately 45% (34). Of all DSM-IV disorders, bipolar disorder has the highest rate of alcohol abuse (35).

In addition to the impact of the increased prevalence of cardiometabolic risk factors in bipolar disorder, it should also be noted that many patients with bipolar disorder suffer chronic depressive symptoms and as a result, will find it difficult to implement lifestyle changes such as exercise, healthy eating and smoking cessation (32).

### **Improving Cardiometabolic Health in Bipolar Disorder**

Bipolar disorder is managed predominately in the specialist mental health services setting. Although this holds many advantages in terms of psychiatric treatment and outcomes, the current absence of integrated psychiatric and medical services may contribute to underrecognition and undertreatment of cardiometabolic disease (32).

Models of care that allow a much more integrated approach to diagnosing, monitoring and treating medical comorbidity in patients with bipolar disorder, particularly in areas of social and economic deprivation, are likely to be necessary in the future (36). There is evidence that an integrated approach comprising chronic disease management, case management and enhanced multidisciplinary teamwork may improve long-term physical health outcomes for individuals with bipolar disorder and other serious mental illnesses (37).

There is an urgent need for more research into the relationship between bipolar disorder and cardiometabolic disease, at an epidemiological, clinical and genetic level (32). As noted above, mood disorders are increasingly regarded as multisystem conditions that affect immunity and endocrine and vascular pathophysiology (38). Further basic science research could allow improved understanding of the pathophysiology of bipolar disorder and inform translational research into more targeted interventions. Future clinical research could focus on evaluation of integrated medical and psychiatric services, as well as identifying targeted approaches for vulnerable groups for medical and psychiatric comorbidity.

## **CONCLUSION**

Cardiometabolic disease is highly prevalent within bipolar disorder and may be a core feature of the diagnosis. It is well documented that physical and mental health problems interact to cause prolonged hospitalisation, treatment failure, poor quality of life and premature mortality. Several recent reports (39-41) in the UK and internationally have highlighted that more integrated services are needed. Further epidemiological, clinical and basic scientific research, alongside a multidisciplinary focus on improving physical health investigation, diagnosis, treatment and monitoring, is required.

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