

# Call to action regarding the vascular-bipolar link: A report from the Vascular Task Force of the International Society for Bipolar Disorders

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## Abstract

**Objectives:** The association of bipolar disorder with early and excessive cardiovascular disease was identified over a century ago. Nonetheless, the vascular-bipolar link remains underrecognized, particularly with regard to how this link can contribute to our understanding of pathogenesis and treatment.

**Methods:** An international group of experts completed a selective review of the literature, distilling core themes, identifying limitations and gaps in the literature, and highlighting future directions to bridge these gaps.

**Results:** The association between bipolar disorder and vascular disease is large in magnitude, consistent across studies, and independent of confounding variables where assessed. The vascular-bipolar link is multifactorial and is difficult to study given the latency between the onset of bipolar disorder, often in adolescence or early adulthood, and subsequent vascular disease, which usually occurs decades later. As a result, studies have often focused on risk factors for vascular disease or intermediate phenotypes, such as structural and functional vascular imaging measures. There is interest in identifying the most relevant mediators of this relationship, including lifestyle (eg, smoking, diet, exercise), medications, and systemic biological mediators (eg, inflammation). Nonetheless, there is a paucity of treatment studies that deliberately engage these mediators, and thus far no treatment studies have focused on engaging vascular imaging targets.

**Conclusions:** Further research focused on the vascular-bipolar link holds promise for gleaning insights regarding the underlying causes of bipolar disorder, identifying novel treatment approaches, and mitigating disparities in cardiovascular outcomes for people with bipolar disorder.

## KEYWORDS

atherosclerosis, bipolar disorder, cardiovascular disease, prevention, stroke, vascular

## 1 | INTRODUCTION

Vascular disease is an exceedingly common, yet arguably underrecognized source of morbidity and mortality in bipolar disorder. The association between bipolar disorder and vascular disease is large in magnitude, consistent across studies internationally, and independent of confounding variables where assessed. The vascular-bipolar link is multifactorial and is difficult to study given the latency between the onset of bipolar disorder, often in adolescence or early adulthood, and subsequent vascular disease, which usually occurs decades later. As a result, studies have often focused on risk factors for vascular disease or intermediate phenotypes, such as structural and functional vascular imaging measures. While there are multiple relevant mediators of this relationship, including lifestyle (eg, smoking, diet, and exercise), medications, and systemic biological mediators (eg, inflammation), there are few treatment studies that deliberately engage these mediators, and thus far no treatment studies have focused on engaging vascular imaging targets. It is acknowledged that bipolar disorder is not unique with regard to its association with vascular disorder. However, the magnitude of increased risk—and the extent of prematurity—of vascular disorders exceeds what is observed in most other psychiatric conditions. Moreover, vascular risk appears to travel in

family pedigrees of adolescents and adults with bipolar disorder, invoking potential genetic contributors to this link.

Experts from the International Society of Bipolar Disorders Vascular Task Force selectively reviewed the literature to synthesize key findings across several domains relevant to the link between bipolar disorder and vascular disease. In addition, the perspective of stakeholders with lived experience of bipolar disorder was represented by a consumer advocacy leader (AK). This paper addresses disparities in treatment of cardiovascular risk factors (CVRFs) and cardiovascular disease (CVD) among those with bipolar disorder, as well as aspects relevant to special populations. We endeavor to provide a broad overview of multiple domains, and future detailed reviews on subtopics herein are anticipated.

## 2 | NATIONWIDE STUDIES REGARDING CARDIOVASCULAR MORTALITY AND CARDIOVASCULAR DISEASE IN BIPOLAR DISORDER

Bipolar disorder is consistently associated with an elevated risk of cardiovascular mortality. In contrast to the elevated risk of suicide

mortality, which is widely recognized and comprises a core focus of prevention and treatment strategies, excess cardiovascular mortality among people with bipolar disorder is not widely appreciated and is not a core focus of prevention and treatment. Excessive risk of cardiovascular mortality has arguably been best demonstrated in Scandinavian countries with registry data that can be linked to mortality statistics, allowing a population-based assessment of risk. Osby et al assessed mortality in a cohort of 15 386 inpatients with bipolar disorder from 1973 to 1995.<sup>1</sup> Bipolar disorder conferred a substantially increased risk of mortality with a Standardized Mortality Ratio (SMR) of 2.6 with 33% of the excess deaths being due to vascular disease (cardiovascular and cerebrovascular) for which the SMR was 2.2.<sup>1</sup> An elevated risk of cardiovascular mortality was also seen in a Danish registry-based study of 11 648 first admissions for bipolar disorder (SMR of 1.6).<sup>2</sup> A pooled estimate for the SMR for cardiovascular deaths in bipolar disorder for studies published between 1987 and 2007 was 1.9.<sup>3</sup> Cardiovascular SMR may differ according to age; for example, the cardiovascular SMR in a recent population-based cohort study in Sweden was 8 for adults <40 years old and 2.5-4 for adults ≥40 years old.<sup>4</sup> Key mortality studies from 2008 to present are highlighted in Table 1.<sup>4-12</sup>

The highlighted study by Crump et al included both inpatients and outpatients in Sweden, although likely still underascertained bipolar disorder, with 6618 identified cases from a national cohort of 6.5 million.<sup>6</sup> Those with bipolar disorder died 9 years younger than expected and this elevated risk of premature (all cause) mortality persisted after adjusting for age, sociodemographic variables, and substance use. The fully adjusted estimates showed significant associations with death from CVD (HR 2.1, 95% CI 1.9-2.5, for women and 1.7, 95% CI 1.5-2.0, for men). Similar magnitude estimates were seen for mortality from ischemic heart disease and stroke. Interestingly, the risk factors for CVD were not as strongly associated in this sample (HR of 1.7 in women and 1.6 in men for diabetes mellitus, and there was no increase in the risk of hypertension or lipid disorders). When stratified by prior diagnosis of chronic diseases, such as heart disease and diabetes, the hazard ratio for mortality from these diseases associated with bipolar disorder was significantly lower, leading the authors to conclude "better provision of primary care may effectively reduce premature mortality."<sup>6</sup> It has indeed been found that those with bipolar disorder appear undertreated for these CVRFs and that such undertreatment is associated with greater mortality risk.<sup>7</sup>

**TABLE 1** Key studies on cardiovascular mortality in bipolar disorder from past decade

Author year	Sample	Key findings
Almeida et al 2014 <sup>11</sup>	Representative Australian cohort of 37 892 men (N = only 101 with bipolar disorder).	23 of 101 men with bipolar disorder died of CVD (SHR 1.4, 95% CI 0.8-2.1)
Angst et al 2013 <sup>12</sup>	Prospective cohort of 403 patients with mood disorder	SMR for CVD of 1.60 for bipolar II disorder, 1.99 for bipolar I disorder, and 3.17 for mania (without major depression)
Boden et al 2015 <sup>10</sup>	Population-based Swedish cohort after first diagnosis of myocardial infarction (SWEDEHEART n = 209 592, bipolar disorder n = 442)	63% higher overall mortality with bipolar disorder (and schizophrenia) after myocardial infarction, even after adjusting for age, gender, smoking, diabetes, hypertension, heart failure, stroke, peripheral vascular disease, infarction type, Killip classification and biomarker levels, and treatment (acute and preventative)
Castagni et al 2013 <sup>9</sup>	Danish Psychiatric Register (n = 3200 with bipolar disorder) after mean follow-up of 6.6 years.	SMR for CVD of 2.1 (95% CI 1.3-3.5) in bipolar disorder, but based on 15 CVD deaths
Crump et al 2013 <sup>6</sup>	Sample of Swedish inpatients and outpatients of 6 587 036 (n = 6 618 with bipolar disorder).	aHR for CVD of 2.14 (95% CI 1.88-2.45) in women (219 CVD deaths) and 1.73 (95% CI 1.48-2.02) in men (162 CVD deaths) after adjusting for age, marital status, education, employment, income, and substance use disorders
Hayes et al 2017 <sup>5</sup>	Representative UK cohort identified from primary care electronic medical records from 2000 to 2014 (N = 17 314 with bipolar disorder and 219 387 controls matched by age and gender)	Widening overall mortality gap for bipolar disorder over the time period sampled. Total of 59 CVD deaths observed in those with bipolar disorder; health- and behavior-adjusted HR 1.05 (non-significant) for CVD death in bipolar disorder
Laursen et al 2013 <sup>8</sup>	Register-based study from Denmark, Finland, and Sweden (n = 39 375 with bipolar disorder).	SMR for CVD mortality in bipolar disorder range 1.6-2.0 across Nordic countries and gender, life expectancy 11-20 years less
Laursen et al 2014 <sup>7</sup>	Danish registry with 1 061 532 persons (14 317 person years of bipolar disorder follow-up)	Those with bipolar disorder less likely to be treated with cardiovascular medications. In people without prior myocardial infarction or cerebrovascular disease, those with treatment for CVD risk factors had mortality rate ratio of 2.59 (95% CI 1.43-4.69) and those not treated had a mortality rate ratio of 3.39 (95% CI 1.87-6.15)
Westman et al 2013 <sup>4</sup>	Population-based sample of Sweden (n = 17 101 with bipolar disorder) with 20 year follow-up	Mortality rate ratio of 2.03 (95% CI 1.93-2.13) for CVD in bipolar disorder.

Abbreviations: CVD, cardiovascular disease; UK, United Kingdom.

Despite increasing recognition of this disparity, the most recent studies demonstrate that the mortality gap appears to be only widening, even in those nations with the most equitable access to healthcare. A follow-up study by Osby et al in Sweden found that the excess mortality, due to CVD, increased over the period of 1987–2010, most significantly among young adults.<sup>13</sup> A study based in the UK also found that the mortality gap for bipolar disorder rose over the period from 2000 to 2014, with a HR for cardiovascular mortality of 1.9 for the period 2010–2014.<sup>5</sup>

The aforementioned studies were all based on cases of bipolar disorder identified based on health service utilization. Representative population studies, that do not rely on or require treatment seeking, circumvent concerns regarding biased sampling. Such population-based studies also show evidence of excess incidence and premature onset of CVD. For example, a longitudinal study evaluating a 3-year period in a US representative sample (NESARC) showed an elevated incidence of CVD (self-reported physician diagnosis) in individuals with bipolar disorder compared to those with major depressive disorder and controls. After controlling for confounding factors, adults with bipolar I ( $n = 1047$ ) and bipolar II ( $n = 392$ ) disorder were more than twice as likely to report a CVD diagnosis. Onset of CVD occurred at much younger ages among people with bipolar disorder than people without mood disorders (17 years younger for bipolar I disorder, and 14 years younger for bipolar II disorder) and significantly younger even than people with major depressive disorder ( $n = 4396$ ).<sup>14</sup> Of note, only one-quarter of adults with bipolar disorder in this study reported lifetime exposure to antimanic treatment, and such exposure was not associated with increased risk of CVD.

## 2.1 | Future directions

There is consistent and compelling evidence linking bipolar disorder to excess cardiovascular mortality, with the strongest evidence coming from northern European patient registry samples. There is also evidence of increased and premature CVD in representative population samples. There remains a need for mortality studies in bipolar disorder with a more global representation, as well as a need to examine mortality in representative population samples (ie, not solely samples based on health service utilization). Insights generated from such studies would be bolstered by inclusion of a broad spectrum of biological, environmental, and traditional CVRFs.

## 3 | CLINICAL COHORT STUDIES OF CARDIOVASCULAR MORTALITY IN BIPOLAR DISORDER

The above-described nationwide studies have high power to detect differences in cardiovascular mortality, but lack the detailed characterization of bipolar samples possible in clinical cohort studies. One of the earliest studies that reported on CVD mortality in a clinical

sample of patients with bipolar disorder was by Tsuang et al (1980). In a retrospective cohort study of 100 patients admitted for mania in the Iowa Psychiatric Hospital, with up to 40 years of follow-up, there was an increased risk of mortality due to diseases of the circulatory system among women.<sup>15</sup> A report from the International Group for the Study of Lithium-treated patients (IGSLi) using a longitudinal follow-up for an average of 6.8 years, which included 727 patients with unipolar or bipolar disorder treated with lithium, showed that there is an increased mortality risk due to cardiovascular causes in these patients compared with the general population [SMR 7.69 (95% CI 1.58, 22.48)], which appeared to be ameliorated with lithium treatment.<sup>16</sup>

The findings of two convergent studies suggest that greater mood symptom burden confers increased risk for cardiovascular mortality. A longitudinal study that compared cardiovascular mortality in 288 bipolar I and 147 bipolar II patients, with an average follow-up of 16.3 years, found that the manic/hypomanic symptom burden was related to the excess mortality independently from other risk factors (hazard ratio [HR] 1.48, 95% CI 1.16, 1.89,  $P = .002$ ), highlighting a potentially more deleterious effect of manic states in the course of CVD. No medication classes were associated with increased risk, and selective serotonin reuptake inhibitors were associated with decreased risk, of cardiovascular mortality.<sup>17</sup> The association of affective symptom burden with cardiovascular mortality was further assessed in a sample of 1716 patients with bipolar I disorder. The duration of the most severe depressive episode—but not of the most severe manic episode—was related to increased vascular mortality (HR 1.16, 95% CI 1.02, 1.33).<sup>18</sup> These findings were in contrast with a previous longitudinal study that included patients with bipolar, schizoaffective, and major depressive disorder, which did not find an association of the persistence of depressive symptoms and subsequent cardiovascular morbidity over a mean time period of 11 years.<sup>19</sup>

Finally, another longitudinal population-based study comprising 334 bipolar I patients and 334 age- and sex-matched controls from Minnesota (US) assessed the incident risk of fatal and non-fatal myocardial infarction and stroke in a 30-year period. When myocardial infarction and stroke were considered as a composite outcome, there was a significant risk in the unadjusted analysis but it was not retained after controlling for baseline CVRFs.<sup>20</sup> Given the inclusion of multiple covariates despite the small sample size, methodologic limitations render this study inconclusive.

## 3.1 | Future directions

There is great need for long-term longitudinal studies of well-phenotyped prospective samples to better understand how the varied course of illness and treatments received by patients may influence the risk of CVD and related comorbidities. Due to the lag between exposure and outcome, incorporation of putative mediators and intermediate vascular phenotypes/ biomarkers into these study designs would be valuable.

## 4 | TRADITIONAL CARDIOVASCULAR RISK FACTORS

Clinical and epidemiologic studies from multiple countries demonstrate that there is excess prevalence of traditional CVRFs among people with bipolar disorder. Indeed, CVD risk may even be elevated among unaffected first-degree relatives of persons with bipolar disorder.<sup>21,22</sup> Recent meta-analyses confirm increased prevalence and/or incidence rates of obesity,<sup>23</sup> hypertension,<sup>24</sup> diabetes,<sup>25</sup> and cigarette smoking<sup>26</sup> among individuals with bipolar disorder. Summary estimates from these meta-analyses for the associations of bipolar disorder with obesity, hypertension, and diabetes are reported in Table 2 and show stronger associations with type 2 diabetes and obesity than hypertension. The burden of CVRFs may differ internationally, with greater burden of CVRFs in North America as compared to Europe.<sup>25,27</sup> Although increased CVRFs are not unique to bipolar disorder, there is evidence that the prevalence of CVRFs among people with BD is higher not only in comparison to controls but also in comparison to people with major depressive disorder.<sup>28</sup>

In addition to concerns from a physical health perspective, the presence of CVRFs among those with bipolar disorder signals an elevated risk for more severe psychiatric symptoms. For example, obesity in bipolar disorder is associated with greater mood symptom burden.<sup>27,29,30</sup> Remarkably, obesity in bipolar disorder is associated with increased rates of suicide attempts in clinical and epidemiologic studies internationally, in both adults and youth.<sup>27,31-36</sup> Although most findings are retrospective, prospective studies confirm that obesity predicts increased risk for mood episodes,<sup>37,38</sup> and reduced response to treatment (both pharmacologic and psychosocial) of manic and depressive symptoms.<sup>39-41</sup> Although less widely studied, similar findings are observed for other CVRFs including diabetes,<sup>42,43</sup> hypertension,<sup>44</sup> and smoking.<sup>45-48</sup>

CVRFs are also associated with reduced neurocognitive function, particularly in frontal-executive tasks.<sup>49-57</sup> The strength of this association may depend in part on the symptomatic status and on the illness duration/stage.<sup>58,59</sup> Prospective studies indicate that the association among CVRFs, particularly obesity, and impaired cognition is bidirectional.<sup>53,59</sup> The association of smoking with neurocognition is inconsistent, possibly because nicotine has dopaminergic

properties that may counteract any vascular-related neurocognitive risk.<sup>60-62</sup>

Finally, CVRFs are also associated with overall functioning. Many,<sup>42,52,63-65</sup> although not all,<sup>66,67</sup> cross-sectional studies have found that among individuals with bipolar disorder those with, vs without, CVRFs such as obesity, metabolic syndrome, and diabetes had poorer psychosocial functioning and higher rates of disability. Obesity<sup>67</sup> and clinically significant weight gain<sup>66</sup> may predict less improvement in functioning following mood episodes, whereas weight loss may yield improved functioning.<sup>68</sup>

### 4.1 | Future directions

While bipolar disorder is strongly related to a myriad of CVRFs, greater prospective research to discern temporality and mediators is needed. A better understanding of the bidirectional influence of these vascular comorbidities on bipolar disorder could help us understand how they may moderate outcomes and impact treatments. Whereas there are many cohort studies in bipolar disorder that carefully characterize the prospective symptomatic course using repeated measures, there is a paucity of studies that integrate similar repeated measures of CVRFs. Such studies are greatly needed, and would benefit from including measures of lifestyle (see Section 5) and biological (see Section 7) mediators.

## 5 | LIFESTYLE MEDIATORS

Many behaviors associated with bipolar disorder may serve as mediators of risk for vascular disease among individuals with bipolar disorder. These are important to recognize as they may be potentially modifiable and targets for intervention.

Smoking is 2 to 3.5 times more common among persons with bipolar disorder than the general population, with smoking prevalence estimates ranging from 30% to 70%.<sup>26,69</sup> Indeed, smoking may be a risk factor for developing bipolar disorder.<sup>70</sup> Smoking cessation treatment, which may include counseling with or without adjunctive medication, has not been studied in randomized trials in samples with bipolar disorder alone. However, a large randomized controlled trial in which 70% of participants had a mood disorder found that varenicline was

**TABLE 2** Summary results from meta-analysis on the associations between cardiovascular risk factors and bipolar disorder

Author	Risk factor	Sample	Summary finding
Alyerbe et al 2018 <sup>24</sup>	Hypertension	Three population-based studies (Denmark, Taiwan, UK) together comprising more than 1.4 million people.	IRR 1.27 (95% CI 1.15-1.40)
Vancampfort et al 2016 <sup>25</sup>	Type 2 Diabetes Mellitus	Six studies of varied designs and unspecified locations with a combined N = 4688	RR 1.89 (95% CI 1.29-2.77)
Zhao et al 2016 <sup>23</sup>	Obesity	Nine cross-sectional studies spanning several North American, South American, and European countries as well as Korea; N = 12 259 with bipolar disorder and N = 615 490 controls	OR 1.77 (95% CI 1.40-2.23)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; UK, United Kingdom.

more effective than nicotine replacement or bupropion and all active treatments were more effective than placebo.<sup>71</sup> Adverse neuropsychiatric events were infrequent and not more common with active treatment relative to placebo.<sup>71</sup> Preliminary findings from a study of 65 outpatients with schizophrenia, schizoaffective disorder, or bipolar disorder found that varenicline improves Framingham estimates of cardiovascular risk, despite the fact that relapse to smoking is common as is substantial weight gain among those with sustained remission.<sup>72</sup>

Sleep disturbances are a risk factor for CVRFs such as obesity and hypertension, and are also common in individuals with bipolar disorder in all phases of illness including remission. In one study, 55% of an interepisode sample with bipolar disorder met diagnostic criteria for insomnia.<sup>73</sup> Sleep disturbances are associated with weight gain,<sup>74</sup> and among individuals with bipolar disorder, with more severe mood symptomatology and poorer treatment response.<sup>75</sup> Thus, addressing sleep disturbances could be an adjunctive intervention to reduce cardiovascular risk, although this has not been studied. For patients with sleep disturbance, pharmacotherapy (ie, melatonin or melatonin agonists)<sup>76,77</sup> and psychosocial interventions can be helpful. For example, those whose sleep disturbances remain refractory could benefit from interpersonal and social rhythms therapy or a bipolar-specific modification of cognitive-behavioral therapy for insomnia (CBTi-BP), which involves regularizing bedtime and rise times, stimulus control, and cautious use of sleep restriction.

Individuals with bipolar disorder are also more likely to have poor dietary and nutritional habits.<sup>78,79</sup> Up to 30% of people with bipolar disorder report binge-eating behavior, which is associated with metabolic risk independent of its effect on obesity.<sup>80</sup> Moreover, binge-eating behavior is a predictor for weight gain following treatment with quetiapine.<sup>81</sup> In addition, several studies suggest that individuals with bipolar disorder are more likely to consume only one meal per day,<sup>79</sup> a high-fat and low-fiber diet,<sup>82</sup> more saturated fat,<sup>83</sup> more sucrose and sweetened beverages,<sup>84</sup> and add more salt to their food.<sup>85</sup> While the findings relating to nutrition are generally convergent, there are exceptions, such as a study reporting that people with bipolar disorder reported consuming fewer calories, including from carbohydrates and fats, and more fiber, than historical controls—despite having twice the prevalence of metabolic syndrome.<sup>86</sup> Mood states and mood symptom burden may explain in part these inconsistencies. In addition, evening chronotype may be associated with significantly higher rates of both binge eating and unhealthy eating habits.<sup>87</sup>

The estimated prevalence of a sedentary lifestyle is between 40% and 65% in people with bipolar disorder.<sup>88</sup> Greater age and greater BMI are associated with particularly low levels of physical activity among individuals with bipolar disorder.<sup>89</sup> Samples with bipolar disorder also demonstrate a diminished functional exercise capacity, with poor exercise test performance related to depressive symptoms and musculoskeletal complaints.<sup>90</sup> Greater physical activity is also associated with a reduced burden of depressive symptoms, better quality of life, better overall function, but a greater burden of manic symptomatology.<sup>88,91</sup> There is reason to believe that exercise may improve mood.<sup>92,93</sup> In a sample with unipolar depression, exercising 45 min/day for 3 days/week was as effective in reducing depressive

symptoms as 50-200 mg flexibly dosed sertraline at 16 weeks, with a lower risk of recurrence over long-term (10 month) follow-up.<sup>94,95</sup> Non-randomized pilot data in bipolar disorder are encouraging.<sup>96</sup> Exercise also appears to increase brain-derived neurotrophic factor (BDNF) levels in women but not men with bipolar disorder,<sup>97</sup> leading some to hypothesize that exercise promotes neurogenesis.<sup>98</sup>

While there exist a variety of pharmacological and lifestyle interventions seeking to optimize nutrition/diet and/or physical activity in the general population, attempts to study or adapt these interventions for those with bipolar or related disorders have been limited. A pilot study of integrated medical and outpatient psychiatric care for bipolar disorder that included focus on sleep/wake rhythms, nutrition, and exercise improved function and reduced psychiatric hospitalizations; however, this study did not report on the impact on risk factors for CVD.<sup>99</sup> A larger study targeting a broader sample with serious mental illness (22% bipolar disorder) found that individually tailored weight management with group exercise sessions resulted in a 3.2 kg greater weight loss at 18 months relative to controls.<sup>100</sup> A lifestyle intervention developed specifically for bipolar disorder, the Nutrition, Exercise, and Wellness intervention (NEW Tx) for bipolar disorder, combines established nutrition/diet and exercise strategies from the general population tailored for those with serious mental illness. Preliminary evidence suggests that the intervention is feasible and acceptable and may encourage exercise in those with bipolar disorder.<sup>101,102</sup>

## 5.1 | Future directions

There is a need to directly evaluate smoking cessation interventions in samples with bipolar disorder, which have unique risks such as treatment-emergent mania. Preliminary evidence of exercise as a treatment for bipolar disorder is a promising area for future research; it is remarkable that there are thus far no published clinical trials that target aerobic/cardiorespiratory fitness in bipolar disorder. Several effective treatments targeting lifestyle have been developed in the general population, but there is a great need to develop treatments tailored for bipolar disorder specifically, rather than “off the shelf” general population approaches that do not adequately integrate such themes as mood symptoms and medication side-effects. From a methodologic perspective, studies that incorporate objective measures of sleep and physical activity (eg, accelerometry) and that move beyond simple self-reports of nutrition and diet are needed.

## 6 | MEDICATIONS AND THE VASCULAR-BIPOLAR LINK

### 6.1 | Association of psychotropic medications with cardiovascular disease and cardiovascular risk factors

The medications commonly used to treat bipolar disorder adversely affect CVRFs with the potential for substantial changes in weight or other risk factors<sup>103</sup> (Note: while various psychotropic medications have



cardiovascular side-effects and/or risks such as arrhythmia, hypertensive crisis, and orthostatic hypotension,<sup>104</sup> the focus of the current article is on atherosclerotic CVD). Widely considered the first-line mood stabilizer, lithium has been associated with weight gain, but is likely associated with less weight gain than valproate or antipsychotics.<sup>105</sup> Lamotrigine or carbamazepine do not commonly induce substantive changes in weight.<sup>106,107</sup> Antipsychotics, particularly second-generation antipsychotics (SGAs), are known to promote weight gain. Clozapine, olanzapine, iloperidone, chlorpromazine, sertindole, quetiapine, risperidone, and paliperidone appear to confer the greatest risk for weight gain.<sup>103</sup> The lowest potential for weight gain is seen with ziprasidone, lurasidone, and cariprazine.<sup>103</sup> Aripiprazole is sometimes also listed as lower in risk, although study results have varied. Aripiprazole is associated with at least double the weight gain observed for adult patients taking mood stabilizers,<sup>108</sup> and is associated with greater weight gain vs placebo in short-term studies of youth with bipolar disorder.<sup>109</sup>

Overall, the general propensity of mood stabilizers and antipsychotics to increase the risk of CVRFs underscores the importance of routine monitoring for weight gain and other adverse cardiometabolic side-effects and appropriate early action where needed. Clearly, treatment-related CVRFs should be minimized in a population at excessive risk. However, it is important to acknowledge that despite the clearly increased risk of CVRFs from many psychotropic medications, there is not definitive evidence that these medications independently increase the risk of CVD among people with bipolar disorder, and some evidence to refute that hypothesis. The PRIMROSE study found that SGAs are not associated with CVD mortality among people with serious mental illness (including schizophrenia, bipolar disorder, or other non-organic psychosis).<sup>110</sup> Even clozapine, perhaps the worst among contemporary psychotropic medications in terms of adversely affecting CVRFs, is associated with reduced mortality, particularly when used consistently.<sup>111</sup> A recent study of 62 250 Finnish adults with schizophrenia followed for a mean of 14.1 years found that antipsychotics are not associated with cardiovascular hospitalization; moreover, the adjusted hazard ratio for cardiovascular mortality for those taking antipsychotics was 0.62.<sup>112</sup> How can this be? Improved symptom control may enable better health-related behaviors and health service utilization, and indirectly impact cardiovascular health. But there may also be more direct vascular-related effects of antipsychotics. Aside from dopamine-related properties of antipsychotics, these medications are pleiotropic, and are associated with reduced inflammation, nitric oxide release, calcium homeostasis, and other mechanisms that may mitigate the cardiovascular risk of these medications.<sup>113-115</sup> Such paradoxical associations have also been observed for statins, which reduce cardiovascular risk despite an association with diabetes.<sup>116</sup> A meta-analysis of long-term ( $\geq 1$  year) trials of antipsychotics did not show any differences in risk for myocardial infarction, stroke, or cardiovascular death.<sup>117</sup>

## 6.2 | Potential role of vascular-related medications as repurposed treatments for bipolar disorder

It has been suggested that the bidirectional associations between CVD and bipolar disorder may represent a pathophysiological nexus

and thus a potential opportunity to repurpose medications traditionally used in the treatment of CVD for bipolar disorder.<sup>118</sup> Statins, a class of medications that are 3-hydroxy-3-methylglutaryl-CoA (HmG CoA) reductase inhibitors, have generated interest in terms of preventing and/or treating depression, perhaps by mitigating the negative effects of inflammation and low density lipoprotein cholesterol on mood.<sup>119-123</sup> A meta-analysis of 3 small clinical trials (total  $n = 165$ ) involving augmentation of SSRI treatment of depression with a statin estimated a net benefit (SMD = 0.73) of statin use on depression.<sup>124</sup> A larger meta-analysis of statin trials found no effect for overall psychological well-being (7 trials with total  $n = 2105$ ), but a sensitivity analysis of the 5 trials analyzing depression showed significant improvements (SMD = 0.43).<sup>125</sup> However, we are not aware of any studies in bipolar disorder samples. Future treatment studies would need to take cholesterol levels into consideration, given prior evidence that low cholesterol levels may be associated with depression, mania, suicidality, impulsivity, aggression, and mortality.<sup>126-129</sup>

There has been similar interest in a potential therapeutic role for antihypertensives in the treatment of mood disorders, including bipolar disorder. While some observational studies of calcium channel blockers are encouraging, a meta-analysis of 6 RCTs of verapamil for mania did not show any significant benefit.<sup>130</sup> Candidate gene studies suggested a potential role for polymorphisms in angiotensin converting enzyme (ACE) in bipolar disorder.<sup>131,132</sup> Relative to other antihypertensive treatments, ACE inhibitors were associated with a lower risk for hospital admission for mood disorders from a large hospital database.<sup>133</sup> A meta-analysis of 11 trials further suggested a significant, but potentially negligible (SMD  $\leq 0.15$ ), effect of ACE inhibitors and angiotensin receptor antagonists on psychological well-being,<sup>134</sup> although these studies were not specifically designed for this purpose.

## 6.3 | Future directions

Several medications used to treat bipolar disorder carry a substantial risk for cardiometabolic side-effects. There is considerable individual variability in vulnerability to these side-effects; their improved prediction could inform stratification for preventive interventions (eg, lifestyle interventions, metformin, etc). While the extant evidence is not yet strong enough to support the routine use of medications used for the treatment of CVRFs to target psychiatric symptomatology in bipolar disorder, there are some interesting findings related to statins and ACE inhibitors that invite rigorous clinical trials.

## 7 | BIOLOGICAL MEDIATORS

There have been numerous peripheral biomarker (ie, derived from blood samples) studies in bipolar disorder, as comprehensively summarized in the ISBD Biomarker Task Force paper.<sup>135</sup> The most

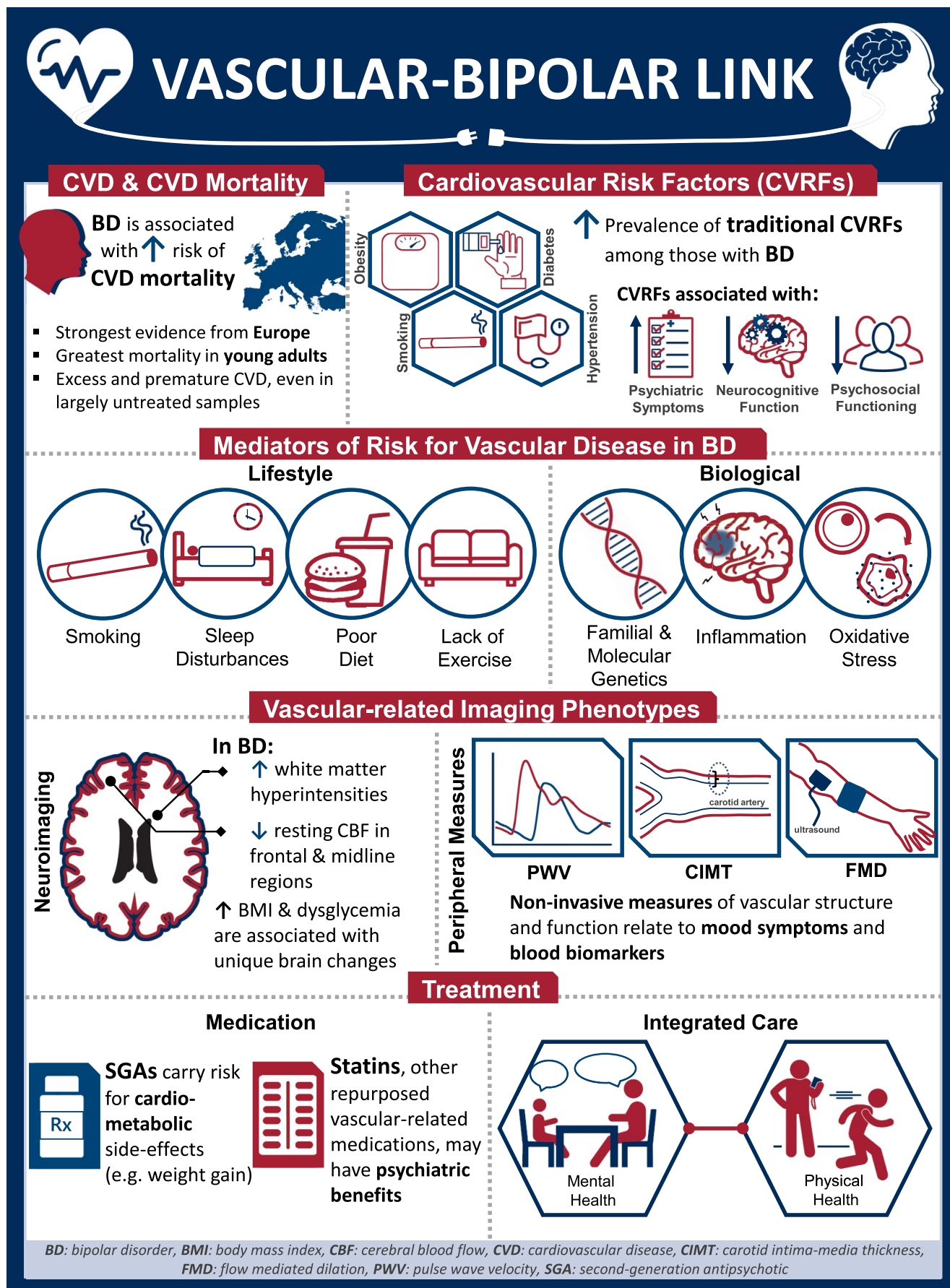


FIGURE 1 Infographic regarding the vascular-bipolar link



frequently studied peripheral biomarkers in bipolar disorder,<sup>135,136</sup> namely, inflammatory markers, oxidative stress markers, and BDNF, are also relevant to CVD. Although other systemic biological mediators may also contribute to the vascular-bipolar link, such as adipokines,<sup>137-139</sup> autonomic dysfunction, and hypothalamic-pituitary-adrenal axis hyperactivation,<sup>140</sup> this section focuses on inflammation, oxidative stress, and BDNF, the putative biological mediators of the vascular-bipolar link for which there is the greatest evidence to date. Moreover, from a treatment perspective, psychotropic medications generally reduce inflammation and oxidative stress, and increase BDNF in clinical and preclinical studies.<sup>135,141</sup>

## 7.1 | Inflammation

Inflammation is associated with incident CVD, traditional CVRFs,<sup>142</sup> and endothelial dysfunction (ED).<sup>143,144</sup> Markers of inflammation, most consistently c-reactive protein (CRP), contribute to the prediction of CVD beyond Framingham risk scores.<sup>142,145</sup> Putative mechanisms of the association between mood disorders and inflammation include glucocorticoid resistance, blood-brain barrier disruption, altered neurotransmitter metabolism, impaired functional connectivity, astrocyte and microglia activation, neuronal damage and degeneration, and reduced neurotrophic support.<sup>146</sup> In adult bipolar disorder, increased frontal cortical inflammation has been observed in postmortem samples<sup>147</sup> and pro-inflammatory genotypes have been implicated.<sup>148</sup> Numerous studies on the topic, including several meta-analyses, confirm that peripheral pro-inflammatory markers are elevated in bipolar disorder, particularly during symptomatic intervals of mania and depression.<sup>149,150</sup>

## 7.2 | Oxidative stress

Oxidative stress, reflecting an imbalance between oxidants and antioxidants, is relevant to vascular function, atherosclerosis, and CVD.<sup>151,152</sup> The interaction of reactive oxygen species with endothelium-derived nitric oxide contributes to ED which in turn is a precursor to atherosclerosis.<sup>153</sup> Oxidative stress-related endothelial damage contributes both to atherosclerotic disease and to metabolic conditions that confer risk for CVD, such as diabetes, dyslipidemia, and hypertension.<sup>154</sup> These effects are, in part, related to shared genetic susceptibility to oxidative stress and CVD.<sup>155</sup> As is common in articles regarding novel therapeutic approaches in bipolar disorder, the concept of therapeutically targeting mitochondrial function for the purpose of reducing oxidative stress is also relevant to CVD.<sup>156</sup> Postmortem studies in bipolar disorder have shown elevated oxidative stress in the brain, especially in frontal regions.<sup>157,158</sup> Similar to the inflammation literature, studies consistently demonstrate elevations of peripheral oxidative stress markers in bipolar disorder, particularly during symptomatic intervals. Oxidative stress has been posited to contribute to neuroprogression.

## 7.3 | BDNF

Whereas the links between CVD and inflammation/oxidative stress are more widely recognized, and perhaps more self-evident, there is also a substantial literature regarding the implications of BDNF.<sup>159</sup> Reduced BDNF levels have been observed in adults suffering from acute coronary syndrome.<sup>160</sup> Serum BDNF levels were inversely associated with CVD and CVD mortality in a prospective study of 3687 Framingham participants, and BDNF genotypic analysis in a related study suggests that the protective effect may be causal.<sup>161</sup> Even in young adults, BDNF levels are associated with vascular function and functional capacity for exercise.<sup>162</sup> Deficiency of BDNF may be implicated in reduced endothelial integrity and increased endothelial cell apoptosis.<sup>163</sup> The BDNF valine to methionine substitution at codon 66 (val66met) polymorphism, associated with reduced function, is associated with bipolar disorder in children and adolescents, and with early-onset bipolar disorder in adults, and may contribute to prefrontal cortical morphometric and metabolic abnormalities in bipolar disorder.<sup>164,165</sup> A systematic review and meta-regression analysis (n = 548 bipolar disorder, n = 565 controls) reported reduced BDNF with large effect sizes (ES) for mania (ES -0.81) and depression (ES -0.97) vs controls.<sup>166</sup> In contrast, differences in BDNF levels among euthymic bipolar disorder patients vs controls were not significant and of modest magnitude (ES -0.20).

## 7.4 | Future directions

While several putative biomarkers have been identified, little is known about the temporal nature of these relationships and/or whether they are causal. Prospective study would be important to discern the relation between these biomarkers and the course of BD and atherosclerosis/CVD. Finally, target-engagement clinical trials are warranted to evaluate whether modifying these biomarkers has an influence on the development and/or progression of CVD.

# 8 | VASCULAR-RELATED NEUROIMAGING

## 8.1 | Leukoaraiosis/white matter hyperintensities

Hyperintensities in brain MRI are thought to reflect focal ischemic damage. Increased rates of white matter hyperintensities (WMH), also described as leukoaraiosis, is among the most consistent structural neuroimaging findings in bipolar disorder.<sup>167,168</sup> While described as non-specific with regard to underlying cause, leukoaraiosis is often considered a manifestation of cerebral small vessel disease, and is an independent predictor of stroke and dementia.<sup>169</sup> Meta-analysis of 27 studies found significantly increased rates of deep WMH among those with bipolar disorder compared to controls (OR 3.2, 95% CI 2.2, 4.5).<sup>170</sup> Rates of overall MRI hyperintensities were numerically but non-significantly higher in bipolar disorder than in major depressive disorder (OR 1.6, 95% CI 0.9-2.7) and schizophrenia (OR 1.5, 95%

CI 0.9, 2.7). The risk of hyperintensities relative to controls was greatest in youth (OR 5.7, 95% CI 2.3, 13.7). There is evidence that WMH burden is related to familiarity and bipolar disorder subtypes,<sup>171</sup> although findings in relatives of people with bipolar disorder are inconsistent.<sup>172</sup> Despite questions regarding whether the association between bipolar disorder and WMH is explained in part by comorbidities such as migraine, developmental disorders, and/or CVRFs,<sup>173</sup> the consistency of increased WMH in bipolar disorder alongside the association of WMH with systemic and cerebral vascular disease indicates the need for continued research on this topic.

## 8.2 | Neuroimaging correlates of cardiovascular risk factors

Obesity among otherwise healthy people is associated with significantly lower total brain volume, particularly lower grey matter volume,<sup>174-179</sup> and with greater brain volume loss over time.<sup>180</sup> These findings have led a number of research groups to investigate whether obesity is associated with brain changes in bipolar disorder. In a first-episode mania sample, overweight/obese bipolar disorder patients had lower white matter volumes than normal-weight patients, particularly in the frontal and temporal lobes and subcortical white matter.<sup>181,182</sup> A second study, also in first-episode mania patients, reported lower temporal-parietal-occipital white matter integrity in overweight/obese compared to normal-weight patients.<sup>183</sup> BMI-related gray matter reductions have also been detected early in the course of bipolar disorder. In an adolescent bipolar disorder sample, higher BMI was associated with lower orbitofrontal cortical and prefrontal cortical thickness.<sup>184</sup> Brain chemistry has been less well studied. In one first-episode mania sample, higher BMI predicted greater hippocampal glutamate and lower hippocampal N-acetylaspartate (NAA) in bipolar disorder patients.<sup>185,186</sup> Interestingly, this was independent of any effect of BMI on hippocampal volumes, since two separate groups reported that hippocampal volume did not vary with BMI in bipolar disorder patients.<sup>186,187</sup> That BMI-related brain changes were located primarily in limbic brain areas, and that they were detected in bipolar disorder patients but not age- and gender-matched control subjects, suggests that higher BMI is associated with unique brain changes in bipolar disorder, such that frontal/temporal limbic brain changes characteristic of bipolar disorder are more pronounced with higher BMI. In keeping with this hypothesis, the only prospective study to date found that first-episode mania patients with clinically significant weight gain ( $\geq 7\%$  of baseline weight) over 12 months also had significantly greater volume loss in the left anterior cingulate gyrus, orbitofrontal cortex, and middle temporal gyrus over the same time period.<sup>188</sup> However, the observational nature of the study precludes definitive conclusions regarding the direction of the observed associations. Moreover, "third variable" causes such as genes that impact both BMI and limbic brain structure/function cannot be excluded.<sup>189-191</sup>

Comparatively fewer studies have examined dysglycemia (ie, diabetes or insulin resistance/glucose intolerance) in relation to neuroimaging phenotypes in bipolar disorder. Hajek and colleagues

reported that dysglycemia among adults with bipolar disorder is associated with lower hippocampal and insular cortex volumes compared to euglycemic adults with bipolar disorder and healthy controls, and is associated with stronger aging effects on hippocampal volumes.<sup>192</sup> A subsequent MR spectroscopy study from the same group found that dysglycemia among adults with bipolar disorder was associated with reduced prefrontal levels of NAA and total creatine compared to euglycemic adults with bipolar disorder and healthy controls; lower levels of these markers were in turn related to poorer global functioning.<sup>193</sup> The relationship between cigarette smoking and neuroimaging findings among individuals with bipolar disorder has also received relatively little attention. We are aware of only one study investigating this relationship, which reported that in a mixed sample of bipolar disorder and schizophrenia patients, smokers had reduced cortical thickness in the left anterior cingulate cortex and insula.<sup>194</sup>

## 8.3 | Cerebral blood flow

An extensive literature has used neuroimaging to examine the function of large-scale neural networks in bipolar disorder, identifying consistent patterns of altered neural response to cognitive and emotional tasks and abnormal coordination of brain activity within and between neural circuits.<sup>195</sup> However, the integrity of the cerebrovascular system, which provides the brain with oxygen and energy substrates, has been comparatively less studied in bipolar disorder. Cerebral blood flow (CBF) is considered an indicator of brain health<sup>196</sup> that is associated with WMH and with systemic vascular risk factors.<sup>197,198</sup> Indeed, CBF has been the most common vascular-related neuroimaging phenotype studied in bipolar disorder. A recent systematic review identified 33 studies with a total of 508 bipolar disorder participants and 538 controls.<sup>199</sup> CBF measurements included single-photon emission computerized tomography (SPECT;  $n = 15$  studies), positron emission tomography (PET;  $n = 8$ ), arterial spin labeling MRI (ASL;  $n = 7$ ), perfusion weighted imaging ( $n = 1$ ), and other approaches ( $n = 2$ ). Most studies of adults with bipolar disorder during episodes of depression or mania found reduced resting CBF in frontal and midline regions vs healthy controls,<sup>200-203</sup> but there were exceptions.<sup>204,205</sup> There was greater inconsistency in findings relating to euthymic bipolar disorder and/or symptomatically heterogeneous groups. Evidence suggests that resting CBF may be most abnormal in those with greater cognitive deficits; Dev et al<sup>206</sup> found that higher resting CBF was associated with better inhibitory performance in the bipolar disorder group but not in the comparison group. Although most studies have examined CBF at rest, several studies have examined changes in CBF as a function of cognitive and/or emotional tasks. For example, Kruger et al found that, following a sad mood provocation task, CBF in medial frontal cortex decreased significantly in bipolar disorder as compared to healthy controls.<sup>207</sup> Most studies that evaluated CBF in bipolar vs unipolar depression have not found significant differences, although one study using pattern recognition analysis found that, despite lack of differences from healthy controls, subgenual anterior cingulate cortex

CBF classified unipolar vs bipolar depression in females with 81% accuracy.<sup>208</sup> Finally, with the exception of a single lithium discontinuation study,<sup>209</sup> there is a paucity of data regarding bipolar disorder treatment and treatment response in relation to CBF and changes therein.

## 8.4 | Future directions

Thus far, there is a gap with regard to the link between neuroimaging phenotypes and hypertension/blood pressure or lipids levels,<sup>55</sup> and related studies are warranted. There are opportunities to capitalize on the advantages of ASL, which magnetically tags blood as a non-invasive endogenous tracer. This offers advantages in general, but particularly in settings where SPECT or PET are not available, and in populations, such as youth and pregnant women, where ionizing radiation should be avoided. Moreover, use of ASL allows for the examination of CBF in relation to other functional and structural MRI phenotypes within the same imaging session. The concept of using vascular-related neuroimaging phenotypes as a treatment target, predictor, and/or moderator has received little attention to date; such a concept may afford insights regarding etiopathology and regarding the use of vascular-related interventions.

## 9 | VASCULAR IMAGING AND FUNCTION

The assessment of vascular function and structure provides an opportunity to investigate intermediate phenotypes, prior to the development of overt vascular disease through surrogate outcomes such as ED. This can facilitate an understanding of how mood symptoms, the course of illness, or treatment of illness may influence risk for vascular disease without waiting for the patient to develop cardiovascular events such as myocardial infarction late in life. Moreover, ED that predates frank atherosclerosis can be mitigated using behavioral and pharmacological approaches (see Section 6).

A few cross-sectional studies have assessed vascular structure and function in adults and adolescents (see Section 10). In adult studies, findings to date have been age dependent. A sample of 27 people with bipolar disorder of a mean age of 32 years did not show any differences compared to matched controls on flow-mediated dilatation (FMD), nitroglycerin-mediated dilation of the brachial artery, pulse-wave velocity (PWV), or augmentation index (AIX).<sup>210</sup> There were also no differences in the reactive hyperemia index or AIX as measured by finger plethysmography in a larger sample of 56 participants with a mean age of 40 years.<sup>211</sup> Another group reported albuterol-induced vasoreactivity deficits among 31 adults (mean age 43 years) with depression; subgroup analyses found significantly lower vasoreactivity among those with unipolar depression ( $n = 11$ ,  $P = .005$ ) but only nominal lower vasoreactivity among those with bipolar depression ( $n = 20$ ,  $P = .086$ ).<sup>212</sup> In another study focused on identifying age-related effects, the older—but not the younger—half of the sample (median split on 32 years) had greater than expected PWV and AIX relative to normative values and this was related to

the retrospectively estimated burden of mood symptoms.<sup>213</sup> In an older sample with mixed mood disorders, lower FMD was seen in those who had a greater burden of mania/hypomania over more than a quarter century of prior follow-up in a prospective cohort.<sup>214</sup>

After an initial study regarding retinal vascular photography in adolescents with bipolar disorder,<sup>215</sup> there have since been several studies on this topic in adults.<sup>216–219</sup> One study found that both adults with bipolar disorder and those with schizophrenia had narrower arterioles and wider venules as compared to healthy volunteers, and adults with bipolar disorder had narrower arterioles and wider venues even as compared to adults with schizophrenia,<sup>216</sup> a pattern generally considered indicative of increased cardiovascular risk.<sup>220</sup>

In summary, non-invasive measures of vascular function and structure may reflect underlying risk factors for vascular disease. The few small studies on vascular function in adults with bipolar disorder have thus far have only detected differences related to bipolar disorder among older adults, and in proportion to the prior burden of mood symptoms. The link between mood symptom burden and vascular risk has also been supported by studies of cardiovascular mortality in bipolar disorder (see Section 2). Preliminary evidence suggests that retinal vascular calibers that are related to cardiovascular risk are worse among people with bipolar disorder than in healthy volunteers or people with schizophrenia.

## 9.1 | Future directions

Non-invasive measures of vascular structure and function afford the opportunity to study an intermediate phenotype to explore mechanisms without waiting until cardiovascular events or mortality occurs. Thus far, most studies have been based on small sample sizes and cross-sectional design. In order to move toward implementing these measures clinically, larger, prospective, repeated-measure studies are needed. Such studies may help identify subgroups for whom these measures are particularly relevant, and would provide a surrogate measure of vascular risk, beyond traditional CVRFs, that may additionally be suited to understanding mechanisms of vascular risk progression overtime and in relation to mood symptoms. In addition to study of medium- and large-caliber vessels, additional studies of microvessels are warranted, such as those involving retinal vascular imaging, and MRI measures of cerebral and cardiac microvessels.

## 10 | SPECIAL POPULATIONS: ELDERLY, YOUTH, AND WOMEN/PREGNANCY

### 10.1 | Bipolar disorder in youth

Similar to adults, the prevalence of traditional CVRFs, and their clustering, is increased in youth with bipolar disorder.<sup>33,34,221,222</sup> There is elevated cardiovascular risk among first- and second-degree relatives of youth with bipolar disorder, particularly among relatives of

youth with familial bipolar disorder.<sup>223</sup> As with adults, obesity among youth with bipolar disorder is associated with greater psychiatric complexity, particularly increased suicide attempts in both clinical and largely untreated epidemiologic samples.<sup>33,34</sup> With regard to CVD-related lifestyle variables, there is increased cigarette smoking, suboptimal nutrition, and eating behaviors, and reduced physical activity, in comparison to healthy youth.<sup>224-226</sup> Traditional CVRFs are negatively associated with executive function among youth with bipolar disorder, an association not observed among healthy youth.<sup>56,57</sup> As with adults, there is evidence that inflammation is elevated and BDNF is reduced in youth with bipolar disorder.<sup>227-229</sup> Studies have also found that BDNF, inflammatory markers, and/or oxidative stress markers are associated with traditional CVRFs as well as with non-invasive ultrasound measures of vascular structure and function.<sup>227,230,231</sup> Preliminary findings from the first retinal photography study in bipolar disorder suggest retinal vascular caliber is associated with blood pressure, peripheral endothelial function, and mood symptoms in youth with bipolar disorder but not among healthy controls.<sup>215</sup> In terms of neuroimaging findings, similar to adults, BMI is negatively associated with cortical volumes and structure, particularly in frontal regions.<sup>184</sup> In contrast to adult studies, there appears to be anomalous elevated CBF in midline and frontal regions among youth with bipolar disorder, although acute aerobic exercise appears to have a temporarily normalizing effect on CBF in youth with bipolar disorder.<sup>184</sup> Finally, there is evidence of reduced cerebrovascular reactivity, as measured using a standard breath-hold paradigm during fMRI, among youth with bipolar disorder, and this is especially evident in periventricular and deep white matter, regions where WMH are commonly observed later in life.<sup>232</sup>

## 10.2 | Bipolar disorder in the elderly

Patients with bipolar disorder begin to have increased risk of cardiovascular and metabolic morbidities in midlife and may die mainly from CVD before reaching geriatric age, with the average cardiovascular mortality occurring 10 years earlier than the general population.<sup>4</sup> In light of this premature mortality, patients with early-onset bipolar disorder who survive into old age probably represent a healthy survivor bipolar disorder subpopulation with favorable outcome. Therefore, studies that focus only on individuals in their 60s and beyond may not be truly representative of the larger bipolar disorder population.<sup>233</sup> A limited number of studies have focused specifically on bipolar disorder in late life. The prevalence of cardiovascular morbidity including hypertension in older-age (>60 years) bipolar disorder (OABD) in existing reports appears to be similar to that in community-based geriatric samples or patients with depressive disorder.<sup>235-238</sup> Furthermore, comparable percentages (about 25%) of older patients with bipolar disorder have coronary heart diseases in Asian and Western reports.<sup>238</sup> However, OABD had significantly higher BMI and a greater burden of endocrine/metabolic diseases.<sup>234,235,237</sup> Consequently, approximately two-thirds of OABD are reported to have a previous stroke or silent cerebral infraction (SCI).<sup>239,240</sup> In

particular, SCIs are detected in 59.5% of OABD, which is dramatically higher than the 20% detected in healthy elderly people.<sup>239</sup> Patients with bipolar disorder, including those with early-onset illness, are at higher risk of cerebrovascular disease in late life. The number of recurrent affective episodes may increase the risk of stroke in OABD with typical-onset age.<sup>239</sup> Cardiovascular morbidity, particularly stroke, may increase with age in OABD and optimal treatment requires awareness of SCI and prevention against recurrent episodes. Among the older (aged >50 years) community-dwelling patients with serious mental illness, given better social functioning and comparable cognitive function in older bipolar patients, they may remain at higher risk for obesity and medical morbidity than schizophrenic ones. Treatments targeting cognitive impairment and CVDs across their life span are necessary.<sup>241</sup>

## 10.3 | Bipolar disorder in women

Emerging evidence suggests that women with bipolar disorder may have a 1.5- to 2.5-fold higher risk for the development of cardiovascular morbidity and for cardiovascular mortality, as compared to women among the general population of Eastern and Western societies.<sup>4,6,242-244</sup> In contrast to the higher risk of CVD in men as compared with premenopausal women in the general population,<sup>245</sup> there is no gender difference in cardiovascular risk among people with bipolar disorder. Overall, it appears that the extent of increased risk of CVD that is conferred by bipolar disorder is accentuated among women. However, one longitudinal (6-year) nationwide cohort study with a relatively younger sample (mean age 36 years) showed that females with bipolar disorder had a lower risk of stroke as compared to males.<sup>246</sup> The difference may result from cardioprotective effects of estrogen.<sup>247</sup> Nevertheless, women with bipolar disorder are more vulnerable to metabolic syndrome<sup>25,248,249</sup> along with and CVD gestational hypertension compared to women without psychiatric disorders.<sup>250,251</sup>

## 10.4 | Future directions

Thus far, studies in different age groups have been mainly cross-sectional, whereas longer-term prospective studies, particularly across key developmental and aging epochs, are needed. Studies of child and adolescent offspring of adults with bipolar disorder are needed, as such study designs are almost uniquely positioned to inform our understanding of the temporal associations between the vascular problems and mood problems to which these offspring are predisposed. Given the known gender differences in the manifestations of, and risk factors for, cardiovascular disorders, future studies should consider gender-related variables (such as sex hormones, and major shifts therein during developmental and reproductive milestones), and should seek to clarify the mechanisms underlying the apparent excessive vascular burden among women with bipolar disorder.

## 11 | DISPARITIES IN CARDIOVASCULAR-RELATED TREATMENT AND NEED FOR INTEGRATED CARE MODELS

There are fundamental disparities in the screening, preventive intervention, and treatment of CVRFs and CVD among people with serious mental illness, including bipolar disorder.<sup>6,252-256</sup> These disparities exist at every conceivable juncture in care (eg, triage, intervention, post-discharge) or lack thereof. These disparities are also ubiquitous, evident in commercial managed care organizations, US Medicare, the US Veterans' Affairs, and population-based data in multiple countries including those with universal healthcare. Finally, these disparities are evident for numerous conditions including diabetes, hypertension, coronary artery disease, congestive heart failure, and stroke. It is worth highlighting a number of specific cardiovascular treatment disparity findings. With regard to hypertension, there appear to be lower rates of screening, prescription, and treatment adherence among people with bipolar disorder.<sup>24</sup> With regard to diabetes care, there are disparities across multiple benchmarks for people with mental illness; effect sizes are especially large among people with bipolar disorder, and are also proportional to the number of psychiatric comorbidities.<sup>257</sup> Finally, with regard to cardiovascular mortality, there is compelling evidence of excess cardiovascular mortality alongside undertreatment at multiple levels, even in countries with comprehensive universal healthcare.<sup>254,258</sup> For example, in Denmark, the increased risk of CVD in bipolar disorder is not reflected in increased treatment contacts for CVD; moreover, even after such contacts are established, there are lower rates of invasive procedures in bipolar disorder. Similar findings are observed in Taiwan, where people with bipolar disorder are half as likely to receive invasive procedures after an acute myocardial infarction.<sup>258</sup> In case the existence of such disparities was not enough to motivate change, there is compelling evidence that if quality of cardiovascular care post-myocardial infarction is equivalent, there is no longer excess mortality associated with having a mental illness.<sup>259</sup> Several studies have sought to evaluate the effectiveness of integrating physical and mental health within a unified treatment model.<sup>260-263</sup> However, such models have not yet been disseminated and/or implemented beyond the original context of a given study, and are therefore not available to most people with bipolar disorder.

### 11.1 | Future directions

The aforementioned disparities are multifactorial, and related to a combination of patient factors, provider factors, and system-level factors. Although preponderance of evidence supports the existence of disparities in care, exceptions exist,<sup>264</sup> and understanding the mechanisms and factors underlying more equitable service delivery models may yield valuable insights. There is an urgent need for more studies evaluating integrated care settings and pathways, particularly in real-world clinical and community settings. Finally, a factor not commonly invoked in discussions of treatment disparities is the premature onset of CVD among people with bipolar disorder;

simply shifting the frame of cardiovascular focus earlier by a decade would better align prevention and early intervention strategies with the epidemiology of CVD in bipolar disorder. One example of such an approach is that of the American Heart Association, which includes bipolar disorder among conditions that confer increased risk for early CVD, and advises earlier screening for, and tighter control of, CVRFs.<sup>140</sup> Another example is the PRIMROSE research program, which demonstrated the superiority of modified risk prediction models for people with severe mental illness over models based solely on traditional CVRFs.<sup>110</sup>

## 12 | CONCLUSIONS

The title of this study declares a call to action. The hope of the authors is that this article has served to make explicit the need for such a call (Figure 1), and to illuminate potential future directions. In an era when there has been a marked *reduction* in cardiovascular mortality in the general population, the excess of burden of cardiovascular mortality among people with bipolar disorder has *increased*. We view this discrepancy as outrageous, not because there is a way to address it but because there are numerous ways to address it. But if we focused this call to action solely on the topic of excess CVD and mortality, we would be missing an opportunity to highlight the relevance of blood vessels to the psychiatric and neurocognitive symptoms that contribute to suffering, functional impairment, and reduced quality of life among people with bipolar disorder, beginning at least as early as adolescence. The call to action is aimed at all those for whom treatment, research, education, and/or lived experience of bipolar disorder are important.

Despite the pernicious features of the vascular-bipolar link, there is also a robust silver lining. How so? Thus far, the treatment of bipolar disorder does not deliberately focus on blood vessels. Given the association of vascular risk factors and disorders with more severe manifestations of bipolar disorder, and given the association of mood symptom burden with vascular disorders and mortality, this raises the question of whether optimizing vascular health can serve to improve mood and cognition. The pipeline of entirely new psychotropic medications has reduced markedly, with little to suggest this will change in the near term. And yet there are evidence-based pharmacological and behavioral approaches that target vascular health and that have not been adequately studied in bipolar disorder. Relatedly, there is a need for treatment studies that intentionally target vascular phenotypes—including the brain, heart, retinal, and peripheral vessels—for the purpose of evaluating the impact of vascular target engagement on standard bipolar disorder outcomes, and for the purpose of informing personalized treatment approaches. There is a need for prospective cohort studies that integrate vascular measures alongside standard psychiatric measures and measures of putative mediators of the vascular-bipolar link. Based on the evidence that the vascular-bipolar link is familial, including relatives in such studies would be an important addition. There is an opportunity for engaging patients and



families in a collaborative effort to minimize the drawbacks and maximize the silver linings of the vascular-bipolar link; knowledge of this link can help those with lived experience advocate for themselves in clinical encounters, and empowers them with the knowledge and hope that optimizing vascular health through lifestyle can benefit both here-and-now mental health and longer-term physical health. Finally, from an antistigma perspective, the vascular-bipolar link can serve to reduce the separation of bipolar disorder from other complex, chronic medical disorders, and can serve to ensure parity in how bipolar disorder and people with bipolar disorder are understood, prioritized, treated, and researched.

In conclusion, progress regarding the vascular-bipolar link will require a more deliberate and systematic integration of vascular metrics in research, treatment approaches, healthcare systems, and education of healthcare professionals and the public. We hope that this article will serve to mobilize a broader spectrum of stakeholders with a vested interest in the vascular-bipolar link, and as such serve as an impetus to accelerate progress. We intend to continue distilling and disseminating the research literature on this topic, including future focused subtopic reviews as the literature and knowledge base continues to accumulate. Finally, we invite any stakeholders who are interested in the vascular-bipolar link to connect with us in order to share ideas and discuss ways to collaboratively encourage and enable action.

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## REFERENCES

- Osby U, Brandt L, Correia N, Ekblom A, Sørensen P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001;58:844-850.
- Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry*. 2007;68:899-907.
- Weiner M, Warren L, Fiedorowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry*. 2011;23:40-47.
- Westman J, Hallgren J, Wahlbeck K, Erlinge D, Alfredsson L, Ösby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. *BMJ Open*. 2013;3:e002373.
- Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *Br J Psychiatry*. 2017;211:175-181.
- Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry*. 2013;70:931-939.
- Laursen TM, Mortensen PB, MacCabe JH, Cohen D, Gasse C. Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study. *Psychol Med*. 2014;44:1625-1637.
- Laursen TM, Wahlbeck K, Hallgren J, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PLoS ONE*. 2013;8:e67133.
- Castagnini A, Foldager L, Bertelsen A. Excess mortality of acute and transient psychotic disorders: comparison with bipolar affective disorder and schizophrenia. *Acta Psychiatr Scand*. 2013;128:370-375.
- Boden R, Molin E, Jernberg T, Kieler H, Lindahl B, Sundström J. Higher mortality after myocardial infarction in patients with

- severe mental illness: a nationwide cohort study. *J Intern Med*. 2015;277:727-736.
11. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Norman PE, Flicker L. Mortality among people with severe mental disorders who reach old age: a longitudinal study of a community-representative sample of 37,892 men. *PLoS ONE*. 2014;9:e111882.
  12. Angst J, Hengartner MP, Gamma A, von Zerssen D, Angst F. Mortality of 403 patients with mood disorders 48 to 52 years after their psychiatric hospitalisation. *Eur Arch Psychiatry Clin Neurosci*. 2013;263:425-434.
  13. Osby U, Westman J, Hallgren J, Gissler M. Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987-2010. *Eur J Public Health*. 2016;26:867-871.
  14. Goldstein BI, Schaffer A, Wang S, Blanco C. Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. *J Clin Psychiatry*. 2015;76:163-169.
  15. Tsuang MT, Woolson RF, Fleming JA. Causes of death in schizophrenia and manic-depression. *Br J Psychiatry*. 1980;136:239-242.
  16. Ahrens B, Grof P, Moller HJ, Muller-Oerlinghausen B, Wolf T. Extended survival of patients on long-term lithium treatment. *Can J Psychiatry*. 1995;40:241-246.
  17. Fiedorowicz JG, Solomon DA, Endicott J, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosom Med*. 2009;71:598-606.
  18. Fiedorowicz JG, Jancic D, Potash JB, Butcher B, Coryell WH. Vascular mortality in participants of a bipolar genomics study. *Psychosomatics*. 2014;55:485-490.
  19. Coryell W, Turvey C, Leon A, et al. Persistence of depressive symptoms and cardiovascular death among patients with affective disorder. *Psychosom Med*. 1999;61:755-761.
  20. Prieto ML, Schenck LA, Kruse JL, et al. Long-term risk of myocardial infarction and stroke in bipolar I disorder: a population-based Cohort Study. *J Affect Disord*. 2016;194:120-127.
  21. Coello K, Kjaerstad HL, Stanislaus S, et al. Thirty-year cardiovascular risk score in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. *Austr NZ J Psychiatry*. 2019;53:651-662.
  22. Tsao W-Y, Hsu J-W, Huang K-L, et al. Risk of cardiometabolic diseases among siblings of patients with bipolar disorder. *J Affect Disord*. 2019;253:171-175.
  23. Zhao Z, Okusaga OO, Quevedo J, Soares JC, Teixeira AL. The potential association between obesity and bipolar disorder: a meta-analysis. *J Affect Disord*. 2016;202:120-123.
  24. Ayerbe L, Forgnone I, Addo J, Siguero A, Gelati S, Ayis S. Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis. *J Affect Disord*. 2018;225:665-670.
  25. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry*. 2016;15:166-174.
  26. Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. *Bipolar Disord*. 2011;13:439-453.
  27. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry*. 2002;63:207-213.
  28. Goldstein BI, Fagioli A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord*. 2009;11:657-662.
  29. Fagioli A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. *J Clin Psychiatry*. 2002;63:528-533.
  30. McIntyre RS, Woldeyohannes HO, Soczynska JK, et al. The rate of metabolic syndrome in euthymic Canadian individuals with bipolar I/II disorder. *Adv Ther*. 2010;27:828-836.
  31. Fagioli A, Kupfer DJ, Rucci P, Scott JA, Novick DM, Frank E. Suicide attempts and ideation in patients with bipolar I disorder. *J Clin Psychiatry*. 2004;65:509-514.
  32. Fagioli A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disord*. 2005;7:424-430.
  33. Shapiro J, Mindra S, Timmins V, et al. Controlled study of obesity among adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2017;27:95-100.
  34. Goldstein BI, Blanco C, He JP, Merikangas K. Correlates of overweight and obesity among adolescents with bipolar disorder in the National Comorbidity Survey-Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2016;55:1020-1026.
  35. Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C. The burden of obesity among adults with bipolar disorder in the United States. *Bipolar Disord*. 2011;13:387-395.
  36. Gomes FA, Kauer-Sant'Anna M, Magalhães PV, et al. Obesity is associated with previous suicide attempts in bipolar disorder. *Acta Neuropsychiatr*. 2010;22:63-67.
  37. Hu C, Torres IJ, Qian H, et al. Trajectories of body mass index change in first episode of mania: 3-year data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *J Affect Disord*. 2017;208:291-297.
  38. Fagioli A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry*. 2003;160:112-117.
  39. McIntyre RSMF, Pappadopoulos E. Baseline metabolic status is a moderator of outcome in bipolar disorder patients: analysis of pooled data from ziprasidone monotherapy clinical trials. 164th Annual Meeting of the American Psychiatric Association. Honolulu, HI: American Psychiatric Association; 2011.
  40. Kemp DE, Gao K, Chan PK, Ganocy SJ, Findling RL, Calabrese JR. Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. *Bipolar Disord*. 2010;12:404-413.
  41. Peters AT, Shesler LW, Sylvia L, et al. Medical burden, body mass index and the outcome of psychosocial interventions for bipolar depression. *Aust NZ J Psychiatry*. 2016;50:667-677.
  42. Ruzickova M, Slaney C, Garnham J, Alda M. Clinical features of bipolar disorder with and without comorbid diabetes mellitus. *Can J Psychiatry*. 2003;48:458-461.
  43. Calkin CV, Ruzickova M, Uher R, et al. Insulin resistance and outcome in bipolar disorder. *Br J Psychiatry*. 2015;206:52-57.
  44. Slomka JM, Piette JD, Post EP, et al. Mood disorder symptoms and elevated cardiovascular disease risk in patients with bipolar disorder. *J Affect Disord*. 2012;138:405-408.
  45. Ickick R, Gard S, Barde M, et al. Physical and mental health burden in cases of bipolar disorder classified as current, former, or non-tobacco smokers. *J Affect Disord*. 2017;208:406-413.
  46. Vanable PA, Carey MP, Carey KB, Maisto SA. Smoking among psychiatric outpatients: relationship to substance use, diagnosis, and illness severity. *Psychol Addict Behav*. 2003;17:259-265.
  47. Waxmonsky JA, Thomas MR, Miklowitz DJ, et al. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. *Gen Hosp Psychiatry*. 2005;27:321-328.
  48. Ostacher MJ, Nierenberg AA, Perlis RH, et al. The relationship between smoking and suicidal behavior, comorbidity, and course of illness in bipolar disorder. *J Clin Psychiatry*. 2006;67:1907-1911.
  49. Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS. The effect of overweight/obesity on

- cognitive function in euthymic individuals with bipolar disorder. *Eur Psychiatry*. 2012;27:223-228.
50. Depp CA, Strassnig M, Mausbach BT, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. *Bipolar Disord*. 2014;16:422-431.
  51. Lackner N, Bengesser SA, Birner A, et al. Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. *World J Biol Psychiatry*. 2016;17:535-546.
  52. Bai YM, Li CT, Tsai SJ, Tu PC, Chen MH, Su TP. Metabolic syndrome and adverse clinical outcomes in patients with bipolar disorder. *BMC Psychiatry*. 2016;16:448.
  53. Mora E, Portella MJ, Martinez-Alonso M, et al. The impact of obesity on cognitive functioning in euthymic bipolar patients: a cross-sectional and longitudinal study. *J Clin Psychiatry*. 2017;78:e924-e932.
  54. Hubenak J, Tuma I, Bazant J. Association of arterial hypertension and cognitive impairment in euthymic bipolar disorder. *Neuro Endocrinol Lett*. 2015;36:294-300.
  55. Bora E, McIntyre RS, Ozerdem A. Neurocognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review. *Psychol Med*. 2019;49:738-749.
  56. Naiberg MR, Newton DF, Collins JE, Bowie CR, Goldstein BI. Impulsivity is associated with blood pressure and waist circumference among adolescents with bipolar disorder. *J Psychiatr Res*. 2016;83:230-239.
  57. Naiberg MR, Newton DF, Collins JE, Dickstein DP, Bowie CR, Goldstein BI. Elevated triglycerides are associated with decreased executive function among adolescents with bipolar disorder. *Acta Psychiatr Scand*. 2016;134:241-248.
  58. Silveira LE, Kozicky JM, Muralidharan K, et al. Neurocognitive functioning in overweight and obese patients with bipolar disorder: data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *Can J Psychiatry*. 2014;59:639-648.
  59. Bond DJ, Torres IJ, Lee SS, et al. Lower cognitive functioning as a predictor of weight gain in bipolar disorder: a 12-month study. *Acta Psychiatr Scand*. 2017;135:239-249.
  60. Depp CA, Bowie CR, Mausbach BT, et al. Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta Psychiatr Scand*. 2015;131:333-341.
  61. Law CW, Soczynska JK, Woldeyohannes HO, Miranda A, Brooks JO 3rd, McIntyre RS. Relation between cigarette smoking and cognitive function in euthymic individuals with bipolar disorder. *Pharmacol Biochem Behav*. 2009;92:12-16.
  62. Morisano D, Wing VC, Sacco KA, Arenovich T, George TP. Effects of tobacco smoking on neuropsychological function in schizophrenia in comparison to other psychiatric disorders and non-psychiatric controls. *Am J Addict*. 2013;22:46-53.
  63. Kolotkin RL, Corey-Lisle PK, Crosby RD, et al. Impact of obesity on health-related quality of life in schizophrenia and bipolar disorder. *Obesity*. 2008;16:749-754.
  64. Calkin C, van de Velde C, Ruzickova M, et al. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disord*. 2009;11:650-656.
  65. Malhotra N, Kulhara P, Chakrabarti S, Grover S. Lifestyle related factors & impact of metabolic syndrome on quality of life, level of functioning & self-esteem in patients with bipolar disorder & schizophrenia. *Indian J Med Res*. 2016;143:434-442.
  66. Bond DJ, Kunz M, Torres IJ, Lam RW, Yatham LN. The association of weight gain with mood symptoms and functional outcomes following a first manic episode: prospective 12-month data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *Bipolar Disord*. 2010;12:616-626.
  67. McElroy SL, Kemp DE, Friedman ES, et al. Obesity, but not metabolic syndrome, negatively affects outcome in bipolar disorder. *Acta Psychiatr Scand*. 2016;133:144-153.
  68. Miller S, Ittasakul P, Wang PW, et al. Enhanced ziprasidone combination therapy effectiveness in obese compared to nonobese patients with bipolar disorder. *J Clin Psychopharmacol*. 2012;32:814-819.
  69. Jackson JG, Diaz FJ, Lopez L, de Leon J. A combined analysis of worldwide studies demonstrates an association between bipolar disorder and tobacco smoking behaviors in adults. *Bipolar Disord*. 2015;17:575-597.
  70. Vermeulen JM, Wootton RE, Treur JL, et al. Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. *Br J Psychiatry*. 2019;1-7. [Epub ahead of print]. <https://doi.org/10.1192/bjp.2019.202>
  71. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387:2507-2520.
  72. Thorndike AN, Achtyes ED, Cather C, et al. Weight gain and 10-year cardiovascular risk with sustained tobacco abstinence in smokers with serious mental illness: a subgroup analysis of a randomized trial. *J Clin Psychiatry*. 2016;77:e320-e326.
  73. Harvey AG, Schmidt DA, Scarna A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *Am J Psychiatry*. 2005;162:50-57.
  74. Cooper CB, Neufeld EV, Dolezal BA, Martin JL. Sleep deprivation and obesity in adults: a brief narrative review. *BMJ Open Sport Exerc Med*. 2018;4:e000392.
  75. Sylvia LG, Chang WC, Kamali M, et al. Sleep disturbance may impact treatment outcome in bipolar disorder: a preliminary investigation in the context of a large comparative effectiveness trial. *J Affect Disord*. 2018;225:563-568.
  76. Norris ER, Karen B, Correll JR, et al. A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. *J Affect Disord*. 2013;144:141-147.
  77. Wang HR, Woo YS, Bahk WM. The role of melatonin and melatonin agonists in counteracting antipsychotic-induced metabolic side effects: a systematic review. *Int Clin Psychopharmacol*. 2016;31:301-306.
  78. Elmslie JL, Mann JI, Silverstone JT, Williams SM, Romans SE. Determinants of overweight and obesity in patients with bipolar disorder. *J Clin Psychiatry*. 2001;62:486-491.
  79. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. *Bipolar Disord*. 2007;9:443-452.
  80. Cuellar-Barboza AB, Winham SJ, Biernacka JM, Frye MA, McElroy SL. Clinical phenotype and genetic risk factors for bipolar disorder with binge eating: an update. *Expert Rev Neurother*. 2019;19:867-879.
  81. Yaramala SR, McElroy SL, Geske J, et al. The impact of binge eating behavior on lithium- and quetiapine-associated changes in body weight, body mass index, and waist circumference during 6 months of treatment: findings from the bipolar CHOICE study. *J Affect Disord*. 2020;266:772-781.
  82. Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychol Med*. 1999;29:697-701.
  83. Ryan M, Collins P, Thakore J. Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psychiatry Res*. 2003;160:284-289.
  84. Elmslie JL, Silverstone JT, Mann JI, Williams SM, Romans SE. Prevalence of overweight and obesity in bipolar patients. *J Clin Psychiatry*. 2000;61:179-184.

85. Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Hyland B. Cardiovascular risk factors for people with mental illness. *Aust N Z J Psychiatry*. 2001;35:196-202.
86. Bly MJ, Taylor SF, Dalack G, et al. Metabolic syndrome in bipolar disorder and schizophrenia: dietary and lifestyle factors compared to the general population. *Bipolar Disord*. 2014;16:277-288.
87. Romo-Nava F, Blom TJ, Guerdjikova A, et al. Evening chronotype, disordered eating behavior, and poor dietary habits in bipolar disorder. *Acta Psychiatr Scand*. 2020. [Epub ahead of print]. <https://doi.org/10.1111/acps.13179>
88. Melo MC, Daher Ede F, Albuquerque SG, de Bruin VM. Exercise in bipolar patients: a systematic review. *J Affect Disord*. 2016;198:32-38.
89. Vancampfort D, Firth J, Schuch F, et al. Physical activity and sedentary behavior in people with bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2016;201:145-152.
90. Vancampfort D, Wyckaert S, Sienaert P, et al. The functional exercise capacity in patients with bipolar disorder versus healthy controls: a pilot study. *Psychiatry Res*. 2015;229:194-199.
91. Sylvia LG, Friedman ES, Kocsis JH, et al. Association of exercise with quality of life and mood symptoms in a comparative effectiveness study of bipolar disorder. *J Affect Disord*. 2013;151:722-727.
92. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ*. 2001;322:763-767.
93. Stathopoulou G, Powers MB, Berry AC, Smits JAJ, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review. *Clin Psychol Sci Pract*. 2006;13:179-193.
94. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med*. 2000;62:633-638.
95. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. *Arch Intern Med*. 1999;159:2349-2356.
96. Ng F, Dodd S, Berk M. The effects of physical activity in the acute treatment of bipolar disorder: a pilot study. *J Affect Disord*. 2007;101:259-262.
97. Schuch FB, da Silveira LE, de Zeni TC, et al. Effects of a single bout of maximal aerobic exercise on BDNF in bipolar disorder: a gender-based response. *Psychiatry Res*. 2015;229:57-62.
98. Sylvia LG, Ametrano RM, Nierenberg AA. Exercise treatment for bipolar disorder: potential mechanisms of action mediated through increased neurogenesis and decreased allostatic load. *Psychother Psychosom*. 2010;79:87-96.
99. Fagioli A, Frank E, Soreca I, Houck PR, Kupfer DJ. Integrating medical and psychiatric care in patients with bipolar disorder. *J Clin Psychopharmacol*. 2008;28:257-258.
100. Daumit GL, Dickerson FB, Wang NY, et al. A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med*. 2013;368:1594-1602.
101. Sylvia LG, Nierenberg AA, Stange JP, Peckham AD, Deckersbach T. Development of an integrated psychosocial treatment to address the medical burden associated with bipolar disorder. *J Psychiatr Pract*. 2011;17:224-232.
102. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, exercise, and wellness treatment in bipolar disorder: proof of concept for a consolidated intervention. *Int J Bipolar Disord*. 2013;1:24.
103. Abosi O, Lopes S, Schmitz S, Fiedorowicz JG. Cardiometabolic effects of psychotropic medications. *Horm Mol Biol Clin Investig*. 2018;36:1-15.
104. Marano G, Traversi G, Romagnoli E, et al. Cardiologic side effects of psychotropic drugs. *J Geriatr Cardiol*. 2011;8:243-253.
105. Bowden CL, Mosolov S, Hranov L, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. *Int Clin Psychopharmacol*. 2010;25:60-67.
106. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64:1013-1024.
107. Chengappa KNR, Chalasani L, Brar JS, Parepally H, Houck P, Levine J. Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review. *Clin Ther*. 2002;24:1576-1584.
108. Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord*. 2009;112:36-49.
109. Almandil NB, Liu Y, Murray ML, Besag FM, Aitchison KJ, Wong IC. Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. *Paediatr Drugs*. 2013;15:139-150.
110. Osborn DPJ, Hardoon S, Omar RZ, et al. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. *JAMA Psychiatry*. 2015;72:143-151.
111. Wimberley T, MacCabe JH, Laursen TM, et al. Mortality and self-harm in Association with clozapine in treatment-resistant schizophrenia. *Am J Psychiatry*. 2017;174:990-998.
112. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry*. 2020;19:61-68.
113. Al-Amin MM, Nasir Uddin MM, Mahmud RH. Effects of antipsychotics on the inflammatory response system of patients with schizophrenia in peripheral blood mononuclear cell cultures. *Clin Psychopharmacol Neurosci*. 2013;11:144-151.
114. Grossini E, Gramaglia C, Farruggio S, et al. Asenapine increases nitric oxide release and protects porcine coronary artery endothelial cells against peroxidation. *Vascu Pharmacol*. 2014;60:127-141.
115. Grossini E, Gramaglia C, Farruggio S, et al. Asenapine modulates nitric oxide release and calcium movements in cardiomyoblasts. *J Pharmacol Pharmacother*. 2016;7:6-14.
116. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ*. 2013;346:f2610.
117. Rotella F, Cassioli E, Calderani E, et al. Long-term metabolic and cardiovascular effects of antipsychotic drugs. A meta-analysis of randomized controlled trials. *Eur Neuropsychopharmacol*. 2020;32:56-65.
118. McIntyre RS. A vision for drug discovery and development: novel targets and multilateral partnerships. *Adv Ther*. 2014;31:245-246.
119. Redlich C, Berk M, Williams LJ, Sundquist J, Sundquist K, Li X. Statin use and risk of depression: a Swedish national cohort study. *BMC Psychiatry*. 2014;14:348.
120. Kim SW, Kang HJ, Bae KY, et al. Interactions between pro-inflammatory cytokines and statins on depression in patients with acute coronary syndrome. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;80:250-254.
121. Persons JE, Robinson JG, Payne ME, Fiedorowicz JG. Serum lipid changes following the onset of depressive symptoms in postmenopausal women. *Psychiatry Res*. 2017;247:282-287.
122. Williams LJ, Pasco JA, Mohebbi M, et al. Statin and aspirin use and the risk of mood disorders among men. *Int J Neuropsychopharmacol*. 2016;19(6):pii:pyw008.



123. Stafford L, Berk M. The use of statins after a cardiac intervention is associated with reduced risk of subsequent depression: proof of concept for the inflammatory and oxidative hypotheses of depression? *J Clin Psychiatry*. 2011;72:1229-1235.
124. Salagre E, Fernandes BS, Dodd S, Brownstein DJ, Berk M. Statins for the treatment of depression: a meta-analysis of randomized, double-blind, placebo-controlled trials. *J Affect Disord*. 2016;200:235-242.
125. O'Neil A, Sanna L, Redlich C, et al. The impact of statins on psychological wellbeing: a systematic review and meta-analysis. *BMC Med*. 2012;10:154.
126. Sung K-C, Huh JH, Ryu S, et al. Low levels of low-density lipoprotein cholesterol and mortality outcomes in non-statin users. *J Clin Med*. 2019;8:1571.
127. Tomson-Johanson K, Harro J. Low cholesterol, impulsivity and violence revisited. *Curr Opin Endocrinol Diabetes Obes*. 2018;25:103-107.
128. Messaoud A, Mensi R, Mrad A, et al. Is low total cholesterol levels associated with suicide attempt in depressive patients? *Ann Gen Psychiatry*. 2017;16:20.
129. Huang Y-J, Tsai S-Y, Chung K-H, Chen P-H, Huang S-H, Kuo C-J. State-dependent alterations of lipid profiles in patients with bipolar disorder. *Int J Psychiatry Med*. 2018;53:273-281.
130. Cipriani A, Saunders K, Attenburrow MJ, et al. A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. *Mol Psychiatry*. 2016;21:1324-1332.
131. Kucukali CI, Aydin M, Ozkok E, et al. Angiotensin-converting enzyme polymorphism in schizophrenia, bipolar disorders, and their first-degree relatives. *Psychiatr Genet*. 2010;20:14-19.
132. Meira-Lima IV, Pereira AC, Mota GF, Krieger JE, Vallada H. Angiotensinogen and angiotensin converting enzyme gene polymorphisms and the risk of bipolar affective disorder in humans. *Neurosci Lett*. 2000;293:103-106.
133. Boal AH, Smith DJ, McCallum L, et al. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. *Hypertension*. 2016;68:1132-1138.
134. Brownstein DJ, Salagre E, Kohler C, et al. Blockade of the angiotensin system improves mental health domain of quality of life: a meta-analysis of randomized clinical trials. *Aust N Z J Psychiatry*. 2018;52:24-38.
135. Frey BN, Andreazza AC, Houenou J, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. *Aust N Z J Psychiatry*. 2013;47:321-332.
136. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011;35:804-817.
137. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci*. 2014;15:6184-6223.
138. Ntaios G, Gatselis NK, Makaritsis K, Dalekos GN. Adipokines as mediators of endothelial function and atherosclerosis. *Atherosclerosis*. 2013;227:216-221.
139. Fernandes BS, Dash S, Jacka F, et al. Leptin in bipolar disorder: a systematic review and meta-analysis. *Eur Psychiatry*. 2016;35:1-7.
140. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132:965-986.
141. Gergerlioglu HS, Savas HA, Bulbul F, Selek S, Uz E, Yumru M. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:697-702.
142. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151:483-495.
143. Glowinska-Olszewska B, Tolwinska J, Urban M. Relationship between endothelial dysfunction, carotid artery intima media thickness and circulating markers of vascular inflammation in obese hypertensive children and adolescents. *J Pediatr Endocrinol Metab*. 2007;20:1125-1136.
144. Liu M, Wang F, Wang Y, Jin R. Atorvastatin improves endothelial function and cardiac performance in patients with dilated cardiomyopathy: the role of inflammation. *Cardiovasc Drugs Ther*. 2009;23:369-376.
145. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation*. 2003;107:499-511.
146. Goldstein BI, Young LT. Toward clinically applicable biomarkers in bipolar disorder: focus on BDNF, inflammatory markers, and endothelial function. *Curr Psychiatry Rep*. 2013;15:425.
147. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol Psychiatry*. 2010;15:384-392.
148. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry*. 2009;70:1078-1090.
149. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116:214-217.
150. Munkholm K, Vinberg M, Vedel KL. Cytokines in bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013;144:16-27.
151. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. *Curr Atheroscler Rep*. 2017;19:42.
152. Forstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. *Circ Res*. 2017;120:713-735.
153. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. 2000;87:840-844.
154. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vasc Pharmacol*. 2018;100:1-19.
155. Huggins GS. Genetic susceptibility to oxidative stress and cardiovascular disease. *EBioMedicine*. 2015;2:1864-1865.
156. Rocha M, Apostolova N, Hernandez-Mijares A, Herance R, Victor VM. Oxidative stress and endothelial dysfunction in cardiovascular disease: mitochondria-targeted therapeutics. *Curr Med Chem*. 2010;17:3827-3841.
157. Andreazza AC, Shao L, Wang J-F, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder/ mitochondrial dysfunction and oxidative stress. *Arch Gen Psychiatry*. 2010;67:360-368.
158. Wang J-F, Shao L, Sun X, Young LT. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. *Bipolar Disord*. 2009;11:523-529.
159. Pius-Sadowska E, Machaliński B. BDNF – a key player in cardiovascular system. *J Mol Cell Cardiol*. 2017;110:54-60.



160. Manni L, Nikolova V, Vyagova D, Chaldakov GN, Aloe L. Reduced plasma levels of NGF and BDNF in patients with acute coronary syndromes. *Int J Cardiol.* 2005;102:169-171.
161. Kaess BM, Preis SR, Lieb W, et al. Circulating brain-derived neurotrophic factor concentrations and the risk of cardiovascular disease in the community. *J Am Heart Assoc.* 2015;4:e001544.
162. Alomari MA, Khabour OF, Maikano A, Alawneh K. Vascular function and brain-derived neurotrophic factor: the functional capacity factor. *Vasc Med.* 2015;20:518-526.
163. Donovan MJ, Lin MI, Wiegand P, et al. Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. *Development.* 2000;127:4531-4540.
164. Tang J, Xiao L, Shu C, et al. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. *Neurosci Lett.* 2008;433:98-102.
165. Matsuo K, Walss-Bass C, Nery FG, et al. Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. *Neuropsychopharmacology.* 2009;34:1904-1913.
166. Fernandes BS, Gama CS, Cereser KM, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. *J Psychiatr Res.* 2011;45:995-1004.
167. Hallahan B, Newell J, Soares JC, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. *Biol Psychiatr.* 2011;69:326-335.
168. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch Gen Psychiatry.* 2008;65:1017-1032.
169. Smith EE. Leukoaraiosis and stroke. *Stroke.* 2010;41:S139-S143.
170. Beyer JL, Young R, Kuchibhatla M, Krishnan KRR. Hyperintense MRI lesions in bipolar disorder: a meta-analysis and review. *Int Rev Psychiatry.* 2009;21:394-409.
171. Tighe SK, Reading SA, Rivkin P, et al. Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives. *Bipolar Disord.* 2012;14:888-893.
172. Gunde E, Novak T, Kopecek M, et al. White matter hyperintensities in affected and unaffected late teenage and early adulthood offspring of bipolar parents: a two-center high-risk study. *J Psychiatr Res.* 2011;45:76-82.
173. Gunde E, Blagdon R, Hajek T. White matter hyperintensities: from medical comorbidities to bipolar disorders and back. *Ann Med.* 2011;43:571-580.
174. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. *BMC Neurol.* 2005;5:23.
175. Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity.* 2008;16:119-124.
176. Gunstad J, Paul RH, Cohen RA, et al. Relationship between body mass index and brain volume in healthy adults. *Int J Neurosci.* 2008;118:1582-1593.
177. Soreca I, Rosano C, Jennings JR, et al. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. *Psychosom Med.* 2009;71:485-490.
178. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp.* 2010;31:1052-1064.
179. Ho AJ, Stein JL, Hua X, et al. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proc Natl Acad Sci USA.* 2010;107:8404-8409.
180. Enzinger C, Fazekas F, Matthews PM, et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology.* 2005;64:1704-1711.
181. Bond DJ, Lang DJ, Noronha MM, et al. The association of elevated body mass index with reduced brain volumes in first-episode mania. *Biol Psychiatr.* 2011;70:381-387.
182. Bond DJ, Ha TH, Lang DJ, et al. Body mass index-related regional gray and white matter volume reductions in first-episode mania patients. *Biol Psychiatr.* 2014;76:138-145.
183. Kuswanto CN, Sum MY, Yang GL, Nowinski WL, McIntyre RS, Sim K. Increased body mass index makes an impact on brain white-matter integrity in adults with remitted first-episode mania. *Psychol Med.* 2014;44:533-541.
184. Islam AH, Metcalfe AWS, MacIntosh BJ, Korczak DJ, Goldstein BI. Greater body mass index is associated with reduced frontal cortical volumes among adolescents with bipolar disorder. *J Psychiatry Neurosci.* 2018;43:120-130.
185. Bond DJ, da Silveira LE, MacMillan EL, et al. Relationship between body mass index and hippocampal glutamate/glutamine in bipolar disorder. *Br J Psychiatry.* 2016;208:146-152.
186. Bond DJ, Silveira LE, MacMillan EL, et al. Diagnosis and body mass index effects on hippocampal volumes and neurochemistry in bipolar disorder. *Transl Psychiatr.* 2017;7:e1071.
187. Viana-Sulzbach M, Pedrini M, Buckner J, Brietzke E, Gama CS. Hippocampus size does not correlate with body mass index in bipolar disorder. *Rev Bras Psiquiatr.* 1999;2016:86-87.
188. Bond DJ, Su W, Honer WG, et al. Weight gain as a predictor of frontal and temporal lobe volume loss in bipolar disorder: a prospective MRI study. *Bipolar Disord.* 2019;21:50-60.
189. Melhorn SJ, Askren MK, Chung WK, et al. FTO genotype impacts food intake and corticolimbic activation. *Am J Clin Nutr.* 2018;107:145-154.
190. Olivo G, Latini F, Wiemerslage L, Larsson EM, Schiöth HB. Disruption of accumbens and thalamic white matter connectivity revealed by diffusion tensor tractography in young men with genetic risk for obesity. *Front Hum Neurosci.* 2018;12:75.
191. Lancaster TM, Ihssen I, Brindley LM, Linden DE. Preliminary evidence for genetic overlap between body mass index and striatal reward response. *Transl Psychiatry.* 2018;8:19.
192. Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. *Neuropsychopharmacology.* 2014;39:2910-2918.
193. Hajek T, Calkin C, Blagdon R, Slaney C, Alda M. Type 2 diabetes mellitus: a potentially modifiable risk factor for neurochemical brain changes in bipolar disorders. *Biol Psychiatr.* 2015;77:295-303.
194. Jørgensen KN, Skjærvø I, Mørch-Johnsen L, et al. Cigarette smoking is associated with thinner cingulate and insular cortices in patients with severe mental illness. *J Psychiatry Neurosci.* 2015;40:241-249.
195. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry.* 2014;171:829-843.
196. Peterson EC, Wang Z, Britz G. Regulation of cerebral blood flow. *Int J Vasc Med.* 2011;2011:823525.
197. Jennings JR, Heim AF, Kuan DC, Gianaros PJ, Muldoon MF, Manuck SB. Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. *Stroke.* 2013;44:2480-2485.
198. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. *J Cereb Blood Flow Metab.* 2016;36:1653-1667.
199. Toma S, MacIntosh BJ, Swardfager W, Goldstein BI. Cerebral blood flow in bipolar disorder: a systematic review. *J Affect Disord.* 2018;241:505-513.
200. Bhardwaj R, Chakrabarti S, Mittal BR, Sharan P. A single photon emission computerized tomography (SPECT) study of regional cerebral blood flow in bipolar disorder. *World J Biol Psychiatry.* 2010;11:334-343.

201. Ito H, Kawashima R, Awata S, et al. Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *J Nucl Med*. 1996;37:410-414.
202. Drevets WC, Price JL, Simpson JR, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997;386:824-827.
203. Rubin E, Sackeim HA, Prohovnik I, Moeller JR, Schnur DB, Mukherjee S. Regional cerebral blood flow in mood disorders: IV. Comparison of mania and depression. *Psychiatry Res*. 1995;61:1-10.
204. Tutus A, Simsek A, Sofuoglu S, et al. Changes in regional cerebral blood flow demonstrated by single photon emission computed tomography in depressive disorders: comparison of unipolar vs. bipolar subtypes. *Psychiatry Res*. 1998;83:169-177.
205. Zhao L, Wang Y, Jia Y, et al. Microstructural abnormalities of basal ganglia and thalamus in bipolar and unipolar disorders: a diffusion kurtosis and perfusion imaging study. *Psychiatry Investig*. 2017;14:471-482.
206. Dev SI, McKenna BS, Sutherland AN, et al. Increased cerebral blood flow associated with better response inhibition in bipolar disorder. *J Int Neuropsychol Soc*. 2015;21:105-115.
207. Krüger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg HS. Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. *Am J Psychiatry*. 2006;163:257-264.
208. Almeida JR, Mourao-Miranda J, Aizenstein HJ, et al. Pattern recognition analysis of anterior cingulate cortex blood flow to classify depression polarity. *Br J Psychiatry*. 2013;203:310-311.
209. Goodwin GM, Cavanagh JTO, Glabus MF, Kehoe RF, O'Carroll RE, Ebmeier KP. Uptake of <sup>99m</sup>Tc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients: associations with mania. *Br J Psychiatry*. 1997;170:426-430.
210. Murray DP, Metz NS, Haynes WG, Fiedorowicz JG. Vascular function is not impaired early in the course of bipolar disorder. *J Psychosom Res*. 2012;72:195-198.
211. Tong B, Abosi O, Schmitz S, Myers J, Pierce GL, Fiedorowicz JG. Bipolar disorder and related mood states are not associated with endothelial function of small arteries in adults without heart disease. *Gen Hosp Psychiatry*. 2018;51:36-40.
212. Rybakowski JK, Wykretowicz A, Heymann-Szlachcinska A, Wysocki H. Impairment of endothelial function in unipolar and bipolar depression. *Biol Psychiatry*. 2006;60:889-891.
213. Sodhi SK, Linder J, Chenard CA, del Miller D, Haynes WG, Fiedorowicz JG. Evidence for accelerated vascular aging in bipolar disorder. *J Psychosom Res*. 2012;73:175-179.
214. Fiedorowicz JG, Coryell WH, Rice JP, Warren LL, Haynes WG. Vasculopathy related to manic/hypomanic symptom burden and first-generation antipsychotics in a sub-sample from the collaborative depression study. *Psychother Psychosom*. 2012;81:235-243.
215. Naiberg MR, Hatch JK, Selkirk B, et al. Retinal photography: a window into the cardiovascular-brain link in adolescent bipolar disorder. *J Affect Disord*. 2017;218:227-237.
216. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular abnormalities in schizophrenia and bipolar disorder: a window to the brain. *Bipolar Disord*. 2019;21:634-641.
217. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular fractal dimension in bipolar disorder and schizophrenia. *J Affect Disord*. 2019;259:98-103.
218. Appaji A, Nagendra B, Chako DM, et al. Examination of retinal vascular trajectory in schizophrenia and bipolar disorder. *Psychiatry Clin Neurosci*. 2019;73:738-744.
219. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular tortuosity in schizophrenia and bipolar disorder. *Schizophr Res*. 2019;212:26-32.
220. Ikram MK, Ong YT, Cheung CY, Wong TY. Retinal vascular caliber measurements: clinical significance, current knowledge and future perspectives. *Ophthalmologica*. 2013;229:125-136.
221. Goldstein BI, Birmaher B, Axelson DA, et al. Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. *J Clin Psychiatry*. 2008;69:1953-1959.
222. Li C, Birmaher B, Rooks B, et al. High prevalence of metabolic syndrome among adolescents and young adults with bipolar disorder. *J Clin Psychiatry*. 2019;80:pil:18m12422.
223. Toma S, Fiksenbaum L, Omrin D, Goldstein BI. Elevated familial cardiovascular burden among adolescents with familial bipolar disorder. *Front Psychiatry*. 2019;10:8.
224. Goldstein BI, Birmaher B, Axelson DA, et al. Significance of cigarette smoking among youths with bipolar disorder. *Am J Addict*. 2008;17:364-371.
225. Martin K, Woo J, Timmins V, et al. Binge eating and emotional eating behaviors among adolescents and young adults with bipolar disorder. *J Affect Disord*. 2016;195:88-95.
226. Jewell L, Abtan R, Scavone A, Timmins V, Swampillai B, Goldstein BI. Preliminary evidence of disparities in physical activity among adolescents with bipolar disorder. *Ment Health Phys Act*. 2015;8:62-67.
227. Hatch JK, Scola G, Olowoyeye O, et al. Inflammatory markers and brain-derived neurotrophic factor as potential bridges linking bipolar disorder and cardiovascular risk among adolescents. *J Clin Psychiatry*. 2017;78:e286-e293.
228. Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. *J Am Acad Child Adolesc Psychiatry*. 2008;47:1077-1085.
229. Goldstein BI, Collinger KA, Lotrich F, et al. Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. *J Child Adolesc Psychopharmacol*. 2011;21:479-484.
230. Hatch J, Andreadza A, Olowoyeye O, Rezin GT, Moody A, Goldstein BI. Cardiovascular and psychiatric characteristics associated with oxidative stress markers among adolescents with bipolar disorder. *J Psychosom Res*. 2015;79:222-227.
231. Goldstein BI, Lotrich F, Axelson DA, et al. Inflammatory markers among adolescents and young adults with bipolar spectrum disorders. *J Clin Psychiatry*. 2015;76:1556-1563.
232. Urback AL, Metcalfe AW, Korczak DJ, MacIntosh BJ, Goldstein BI. Reduced cerebrovascular reactivity among adolescents with bipolar disorder. *Bipolar Disord*. 2019;21:124-131.
233. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord*. 2015;17:689-704.
234. Dols A, Rhebergen D, Beekman A, Kupka R, Sajatovic M, Stek ML. Psychiatric and medical comorbidities: results from a bipolar elderly cohort study. *Am J Geriatr Psychiatry*. 2014;22:1066-1074.
235. Gildengers AG, Whyte EM, Drayer RA, et al. Medical burden in late-life bipolar and major depressive disorders. *Am J Geriatr Psychiatry*. 2008;16:194-200.
236. Lala SV, Sajatovic M. Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: a literature review. *J Geriatr Psychiatry Neurol*. 2012;25:20-25.
237. Tsai SY, Kuo CJ, Chung KH, Huang YL, Lee HC, Chen CC. Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. *Am J Geriatr Psychiatry*. 2009;17:1004-1011.
238. Chen PH, Gildengers AG, Lee CH, Chen ML, Kuo CJ, Tsai SY. High serum sodium level in affective episode associated with coronary heart disease in old adults with bipolar disorder. *Int J Psychiatry Med*. 2015;50:422-433.
239. Lee H-C, Hsu J-L, Chen P-H, Chung K-H, Huang Y-J, Tsai S-Y. High risk of silent stroke in older bipolar patients with typical-onset age. *Psychogeriatrics*. 2019;19:355-362.

240. Huang S-H, Chung K-H, Hsu J-L, Wu J-Y, Huang Y-L, Tsai S-Y. The risk factors for elderly patients with bipolar disorder having cerebral infarction. *J Geriatr Psychiatry Neurol*. 2012;25:15-19.
241. Liao PC, Chung KH, Chen PH, Kuo CJ, Huang YJ, Tsai SY. Differences in outcomes between older community-dwelling patients with bipolar disorder and schizophrenia with illness onset at young age. *Psychogeriatrics*. 2020. <https://doi.org/10.1111/psyg.12514>
242. Wu SI, Chen SC, Liu SI, et al. Relative risk of acute myocardial infarction in people with schizophrenia and bipolar disorder: a Population-Based Cohort Study. *PLoS ONE*. 2015;10:e0134763.
243. Jackson CA, Kerssens J, Fleetwood K, Smith DJ, Mercer SW, Wild SH. Incidence of ischaemic heart disease and stroke among people with psychiatric disorders: retrospective cohort study. *Br J Psychiatry*. 2019;1-8. <https://doi.org/10.1192/bjp.2019.250>.
244. Vance MC, Wiitala WL, Sussman JB, Pfeiffer P, Hayward RA. Increased cardiovascular disease risk in veterans with mental illness. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005563.
245. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics-2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.
246. Lin HC, Tsai SY, Lee HC. Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. *J Affect Disord*. 2007;100:49-54.
247. Simon M, Boutouyrie P, Narayanan K, et al. Sex disparities in ideal cardiovascular health. *Heart*. 2017;103:1595-1601.
248. Baskaran A, Cha DS, Powell AM, Jalil D, McIntyre RS. Sex differences in rates of obesity in bipolar disorder: postulated mechanisms. *Bipolar Disord*. 2014;16:83-92.
249. Reininghaus B, Riedrich K, Dalkner N, et al. Physical health in individuals with psychiatric disorders in Austria. *J Affect Disord*. 2019;257:38-44.
250. Lee HC, Lin HC. Maternal bipolar disorder increased low birth-weight and preterm births: a nationwide population-based study. *J Affect Disord*. 2010;121:100-105.
251. Auger N, Potter BJ, Healy-Profitts J, He S, Schnitzer ME, Paradis G. Mood disorders in pregnant women and future cardiovascular risk. *J Affect Disord*. 2020;266:128-134.
252. Hippisley-Cox J, Parker C, Coupland C, et al. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart*. 2007;93:1256-1262.
253. Vinogradova Y, Coupland C, Hippisley-Cox J, Whyte S, Penny C. Effects of severe mental illness on survival of people with diabetes. *Br J Psychiatry*. 2010;197:272-277.
254. Laursen T, Munk-Olsen T, Agerbo E, Gasse C, Mortensen P. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry*. 2009;66:713-720.
255. Atzema CL, Schull MJ, Tu JV. The effect of a charted history of depression on emergency department triage and outcomes in patients with acute myocardial infarction. *Can Med Assoc J*. 2011;183:663-669.
256. Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. *JAMA*. 2000;283:506-511.
257. Frayne SM, Halanych JH, Miller DR, et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med*. 2005;165:2631-2638.
258. Wu SI, Chen SC, Juang JJ, et al. Diagnostic procedures, revascularization, and inpatient mortality after acute myocardial infarction in patients with schizophrenia and bipolar disorder. *Psychosom Med*. 2013;75:52-59.
259. Druss BG, Bradford WD, Rosenheck RA, Radford MJ, Krumholz HM. Quality of medical care and excess mortality in older patients with mental disorders. *Arch Gen Psychiatry*. 2001;58:565-572.
260. Fagioli A, Frank E, Soreca I, et al. Integrating medical and psychiatric care in patients with bipolar disorder. *J Clin Psychopharmacol*. 2008;28:257-258.
261. Kilbourne AM, Goodrich DE, Lai Z, et al. Randomized controlled trial to reduce cardiovascular disease risk for patients with bipolar disorder: the Self-Management Addressing Heart Risk Trial (SMAHRT). *J Clin psychiatry*. 2013;74:e655-e662.
262. Druss BG, von Esenwein SA, Compton MT, Rask KJ, Zhao L, Parker RM. A randomized trial of medical care management for community mental health settings: the Primary Care Access, Referral, and Evaluation (PCARE) study. *Am J Psychiatry*. 2010;167(2):151-159.
263. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2010;363:2611-2620.
264. Whyte S, Penny C, Phelan M, Hippisley-Cox J, Majeed A. Quality of diabetes care in patients with schizophrenia and bipolar disorder: cross-sectional study. *Diabet Med*. 2007;24:1442-1448.

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