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Course of illness and the development of vascular disease in individuals with bipolar disorder

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COURSE OF ILLNESS AND THE DEVELOPMENT OF VASCULAR DISEASE IN INDIVIDUALS WITH BIPOLAR DISORDER

by

Jess G. Fiedorowicz

An Abstract

A thesis submitted in partial fulfillment of the
requirements for the Doctor of Philosophy degree
in Translational Biomedicine in
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Thesis Supervisor: Professor William G. Haynes

ABSTRACT

For over a century, there have been suggestions of a link between what is currently called bipolar disorder and cardiovascular mortality. In the contemporary epidemiological literature, this risk has been confirmed and approximates twice that expected based on age and gender. To date, however, this information has come primarily from clinical samples, which carry considerable risk of selection bias. The studies contained in this dissertation sought to assess this relationship using methods less vulnerable to selection bias and to determine the role that course of illness and treatments for illness may play in the development of vascular disease. In a nationally representative sample, we confirmed a link between mood disorders and vascular disease, which was particularly pronounced in women with bipolar disorder. In subsequent studies, a dose-response relationship between the duration of clinically significant hypomanic or manic symptoms and both cardiovascular mortality and endothelial function was seen. While medication exposure did not appear related to mortality or endothelial function, first generation antipsychotics were associated with arterial stiffness, an effect apparently mediated by elevations in blood pressure. In cross-sectional samples, our data suggests that vasculopathy is not present early in the course of bipolar disorder although is much greater than expected later in the course of illness. This dissertation purports that vasculopathy develops over the long-term course of bipolar disorder, is proportional to symptom burden, and is influenced by health behaviors and treatments. These findings may provide opportunities for clinicians and those afflicted to intervene to address this excess risk of vascular morbidity and mortality.

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CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

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has been approved by the Examining Committee for the thesis requirement for the Doctor of Philosophy degree in Translational Biomedicine at the December 2011 graduation.

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Several of the studies encompassed by this dissertation have been published in the medical literature. This material has been adapted for this dissertation and its thesis though similarities between these chapters and published material will invariably exist and are construed to constitute fair use. Chapter 1 specifically includes material from Weiner M et al. *Annals of Clinical Psychiatry* 2011 and Murray DM et al. *Current Psychiatry Reports* 2009. Chapter 2 highlights material from Fiedorowicz JG et al. *Journal of Psychosomatic Research* 2011. Chapter 3 presents material from Fiedorowicz JG et al. *Psychosomatic Medicine* 2009. Chapter 4 represents soon to be published material in *Psychotherapy and Psychosomatics* by Fiedorowicz JG et al.

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LIST OF ABBREVIATIONS

Abbreviations

BMI = Body Mass Index

CDS = Collaborative Depression Study

CIDI = Composite International Diagnostic Interview

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

FMD = Flow-Mediated Dilation

HDL = High Density Lipoprotein

HOMA-IR = Homeostatic Model Assessment for Insulin Resistance

LDL = Low Density Lipoprotein

LIFE = Longitudinal Interval Follow-up Evaluation

NCS-R = National Comorbidity Study – Replication

NTG = Nitroglycerin

PSRs = Psychiatric Status Ratings

PWV = Pulse Wave Velocity

RDC= Research Diagnostic Criteria

SMR = Standardized Mortality Ratio

SSRIs = Selective Serotonin Reuptake Inhibitors

TCAs = Tricyclic Antidepressants

VLDL = Very Low Density Lipoprotein

WMH = World Mental Health

CHAPTER I

BACKGROUND ON VASCULAR RISK IN BIPOLAR AND RELATED AFFECTIVE DISORDERS

History on mortality in bipolar disorder

More than a century ago, case studies of individuals suffering from mental illness provided the first identified information on vascular mortality in manic-depressive or bipolar disorder. Although bipolar disorder had not yet been given its current name, at that time, the cases of mania and the construct of manic-depressive insanity were analogous to the contemporary construct of bipolar disorder.[1] In one of the earliest reports associating mania with sudden, potentially cardiovascular death, Luther Bell reported on 40 cases of mania seen at the McLean Asylum from 1836-1849, more than three-quarters of which ended fatally. A patient suffering from "Bell's mania" was noted to "get so little food, so little sleep, and be exercised with such constant restlessness and anxiety, that he will fall off from day to day… At the expiration of two or three weeks, your patient will sink into death."[2] Although several of the case studies in the report involved patients who recovered completely, the majority ultimately died. Bell compared this illness to delirium tremens, inflammation of the brain and meninges, and "passive congestion" of the cerebral circulation, but found no evidence of these conditions on autopsy and concluded that those experiencing similar manias would be at greater risk of sudden death or were perhaps suffering from an illness distinct from any previously defined.[2] Similar cases were later presented with continued debate about whether these represented sudden death in mania or a distinct condition altogether.[3]

Almost a hundred years later, Irving Derby studied mortality in patients with manic-depression and proclaimed exhaustion as the most common cause of death. Between 1912 and 1932, 980 patients admitted to Brooklyn State Hospital for manic-depression died during their hospitalization. The cause of death for 40% of those patients

was determined to be "exhaustion from acute mental illness," a condition conceivably similar to that described by Bell almost a century earlier. Cardiac disease was the next most common cause of death, resulting in an estimated 31% of deaths. Derby hypothesized that "many of these 'exhaustion' cases appeared . . . to have actually died of somatic disease" with "cardiovascular disturbance" posited as a potential etiology.[4] Interestingly, like Bell, he described "the typical case of exhaustion" as characterized by dehydration, fatigue, increased pulse rate, and "some degree of temperature elevation."[4] Near the same time, in 1947, Adlund generated from a series of case studies the hypothesis that the illness he referred to as acute exhaustive psychoses "originates as a psychogenic problem and that the psychopathology . . . is expressed through dysfunctions of the cardiovascular, heat regulatory, and hematopoietic systems."[5]

These early studies lacked the methodological rigor of systematic observational studies and occurred during a period lacking the clinical methodology upon which to rule-out currently known medical illnesses or draw more definitive diagnoses on autopsy. Further, the symptoms to characterize "acute exhaustive psychoses" (described by varied terms such as Bell's Mania, fatal catatonia, manic-depressive exhaustive deaths, Scheid's cyanotic syndrome, and brain death) would warrant placement of agitated delirium at the top of a physician's differential diagnosis today. These symptoms include disorientation, confusion, visual hallucinations, and fever and were even compared to delirium tremens and typhoid fever at the time of publication,[3,4] conditions that could precipitate and subsequently resemble encephalopathy or delirium. Because of this limitation, these early studies do not solidly support the theory that bipolar disorder and cardiovascular illness are linked, although the link between bipolar disorder and potentially vascular mortality was already a topic of clinical interest and research over a century ago.

Renewing interest in the cardiovascular morbidity and mortality associated with manic-depression, a number of cohort studies reported associations. Two early German publications in 1928 and 1938 suggested that arteriosclerotic disease occurred more often

and earlier in those with manic depression than in the general population.[6-8] Comprehensive studies of state hospital samples were performed in the 1940's and early 1950's. Alstrom studied the death rates of patients with different mental diseases in the New York Civil State Hospitals and compared these rates to the death rates of the general population in New York. He found that the annual death rate of patients with manic depression was twice that of patients with schizophrenia, about 7.7% as compared to 3.2%. Alstrom also estimated that the risk of cardiovascular disease with manic-depression was twice that of the general population.[9] A study by Odegard took mortality information from Norwegian mental hospitals over a period of approximately 15 years. With a sample of 21,522 first admissions for mental diseases, there were 3,370 deaths – a mortality rate five to six times that of the general population. Additionally, Odegard found those with manic-depression had a higher mortality rate than those with schizophrenia. Males and females with schizophrenia had relative mortalities of 3.2 and 4.8 respectively, while males and females with manic-depression had relative mortalities of 3.8 and 6.4, where relative mortality represented the ratio of the sample death rate to that of the normal population. Odegard also observed that excess mortality from circulatory diseases was lower in those with schizophrenia compared to the rest of the mentally ill population and he hypothesized that these individuals "may be protected against circulatory disturbance by their less intensive emotional reactions and their physical inactivity."[10] Malzberg performed a three-part study in which he reviewed the rates of mortality and discharge among first admissions to the New York Civil State Hospital. Malzberg did not stratify results by cause of death or diagnoses, but he concluded that mortality rates were lower for individuals suffering from dementia praecox, now called schizophrenia.[11-13] Overall, these studies illustrated that those admitted to public mental health hospitals had four to ten times the mortality risk of the general population. These studies further identified individuals with what is now termed

bipolar disorder as a group that appeared to be at particular risk, especially regarding cardiovascular disease.

The excess mortality identified by Malzberg, Odegard, and Alstrom were largely attributed to the conditions of public mental health facilities. More than 20 years after the conclusion of Malzberg, Odegard, and Alstrom's studies, Babigian and Odoroff studied mortality in a sample of those treated for mental illness.[14] They assessed the mortality of all patients with psychiatric illness who had been reported to the Monroe County Psychiatric Case Register between 1960 and 1966. This included inpatients and outpatients treated in private and public settings, representing 6% of the residents of Monroe County, New York. This study found that "the relative risk for the registered group, when adjusted for age, sex, marital status, and socioeconomic status, is three times the general population." This study also found four causes of death that were more common in patients with mental illness: circulatory illness, respiratory illness, accidents, and suicide.[14] While the Babigian and Odoroff study's use of a broad clinical sample attenuated the selection bias of prior studies, the potential selection bias persists in the registry. A patient's mental disease may have only been identified because medical treatment was sought for a separate physical illness, making it possible that the sampled case population includes a disproportionate medical burden relative to a more representative population of individuals with mental disorders. This potential selection bias has been dubbed Berkson's bias or Berkson's Paradox.[15] This bias is difficult to avoid, especially when research samples are drawn from those treated in clinical settings. Because of this, Berkson's bias pervades the literature on mortality associated with mental illness[16] though likely fails to explain the full burden of excess mortality.

Contemporary estimates of vascular mortality in bipolar disorder

Contemporary epidemiological studies have consistently found individuals with bipolar disorder to be at an elevated risk for cardiovascular mortality relative to the general population. Less consistent elevations in risk are seen when compared to samples

with unipolar depression. Elevations in mortality are often measured through use of the Standardized Mortality Ratio (SMR). The SMR is the ratio of the number of deaths observed in a sample compared to that would be expected from age-specific rates from a reference population.

An Iowa study by Tsuang et al. included 100 patients with admissions for mania and found an increased risk of cardiovascular mortality in women (SMR = 1.63), but not men.[17] Only 24 deaths from cardiovascular causes were observed in this study, limiting power, and an interaction by gender was not tested. A larger study in Denmark reported a similar estimate for cardiovascular mortality in bipolar disorder when compared to general population estimates (SMR = 1.60).[18] In a prior analysis of a sub-sample from the same Danish Psychiatric Central Registrar, which included patients with bipolar and unipolar depressive disorders, those with bipolar disorder were found to have a significantly increased incidence of cardiovascular mortality as compared to those with unipolar affective disorders.[19]

A UK study published in 1994 also showed a dramatic difference between the expected and observed deaths due to cardiovascular illness in patients with bipolar disorder. During the period of study, which lasted 12-17 years (registration between 1970 and 1975 and assessment in 1987), 57 out of 472 patients died. Of these 57 deaths, 42.1% were due to cardiovascular illness, yet the expected frequency was only 14%. The resultant SMR of 3.0 indicates that for each expected cardiovascular death during the period of study, the expected and another two unexpected cardiovascular deaths occurred.[20] Thus, 2/3 of the observed cardiovascular deaths in this sample could be attributed to the presence of bipolar disorder.

In Zurich, a study by Angst et al. followed 406 patients with bipolar (N = 220) and unipolar (N = 186) depression who were hospitalized between 1959 and 1963 for 34-38 years, at which point 76% of the sample had died. Those with bipolar disorder were more likely to have died from cardiovascular illness than those with unipolar major

depression (SMR for cardiovascular disease of 1.84 for those with bipolar depression vs. 1.36 for those with unipolar depression). Additionally, the patients with bipolar I had higher rates of death due to cardiovascular illness than those with bipolar II.[21] No subsequent study to date has contrasted cardiovascular mortality by bipolar subtype, apart from that reported later in Chapter 3. The diagnosis of bipolar I requires the presence of manic syndromes whereas bipolar II involves hypomanias and depression, which fall short of the diagnostic threshold for mania. The distinction between these bipolar subtypes and unipolar major depression is graphically illustrated in **Figure 1**.

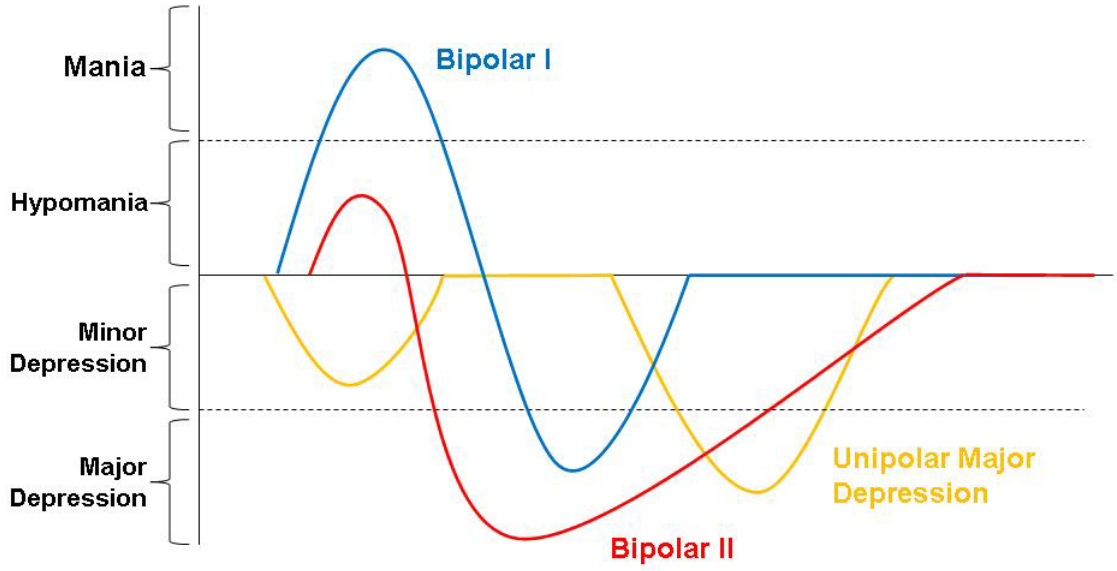

Figure 1. Prototypical Courses of Illness for Bipolar Subtypes in Contrast to Unipolar Major Depression. The course of illness for the bipolar subtypes are distinguished by the more extreme mood elevation syndromes of bipolar I. Individuals with bipolar I have had at least one episode crossing the threshold for mania. Individuals with bipolar II have one or more major depressive episodes with hypomania, but not mania. Adapted from figure created by Tao Zhang.

A cohort study by Laursen et al. of more than 5.5 million Danish people followed from either their 15th birthday or the beginning of 1973 through the beginning of 2001

found that of 11,648 individuals who had been admitted for the first time with a diagnosis of bipolar disorder, 3,669 were deceased by the end of the study period. The SMR for cardiovascular disease in bipolar disorder was 1.59 for men and 1.47 for women.[22] This large study strongly supported prior evidence of excess cardiovascular morbidity for those suffering from bipolar disorder. A similarly designed study of 15,386 individuals with bipolar disorder, representing all patients with a hospital diagnosis from a national register between 1973 and 1995 was conducted by Osby et al. in Sweden. A total of 3,463 deaths were observed among those with a diagnosis of bipolar disorder, resulting in an estimated SMR for cardiovascular deaths of 1.9 for males and 2.6 for women. This was notably higher than the SMR for cardiovascular deaths among individuals with unipolar depression of 1.5 for men and 1.7 for women.[23]

The cohort studies detailed above reporting cardiovascular SMRs for samples with bipolar disorder and published after 2000 are summarized in **Table 1**. This table includes only those studies wherein estimates for samples or sub-samples of individuals exclusively with bipolar disorder could be extracted. One study was not included because it presented composite data from mixed samples.[24]

Potential causes

Any association between bipolar disorder and cardiovascular mortality is undoubtedly complex and may involve the interplay of several factors. Individuals with bipolar and related disorders are less likely to have a primary care physician[25] and may struggle with accessing necessary care. They may also face financial barriers and are more likely to have difficulty maintaining insurance coverage or to find themselves among the uninsured in countries such as the United States, which lacks universal coverage.[26] Even if these access barriers are addressed, individuals may still experience difficulty navigating a complex health care system, underscoring the need for integrated health care services.[25]

Table 1. Standardized Mortality Ratios (SMR) for Cardiovascular Death in Bipolar Disorder

Study Year	Sample	Observed Expected	SMR Female	SMR Male
Osby et al. 2001	Inpatients, Sweden, index admission 1973-1995 (N=15,386)	1073 481.5	2.65	1.94
Angst et al. 2002	Inpatients, Switzerland, index admission 1959-1963 (N=220)	59 31.5	1.84	
Laursen et al. 2007	Inpatients, Denmark, alive on or born after 1973 (N=11,648)	818 502.4	1.67	1.58

Note: The above table summarizes estimates of cardiovascular cause-specific mortality in bipolar disorder. The results from these inpatient samples suggest approximately a doubling of risk. Gender-specific estimates are reported when available. Observed deaths were provided on request for the Laursen et al. study. Studies presenting a SMR for cardiovascular death in bipolar disorder and published after 2000 were selected for inclusion. Adapted from Weiner et al. *Annals of Clinical Psychiatry* 2011.[27]

Maladaptive health behaviors may also contribute to the observed relationship between bipolar disorder and cardiovascular mortality. Individuals with bipolar disorder are much more likely to smoke than the general population and most psychiatric conditions.[28,29] Individuals with bipolar disorder may also be more likely to eat poorly[30] or to be physically inactive.[31]

Medications indicated for the treatment of bipolar disorder may adversely impact cardiovascular risk. Pharmacological treatment includes three broad classes of medications: mood stabilizers, antipsychotics, and antidepressants. Treatments can aim to target acute syndromes such as mania or depression or to prevent such episodes. First-line mood stabilizers include lithium, divalproex, and lamotrigine. Second generation antipsychotics have also demonstrated effectiveness, however, are less desirable for long-term treatment given cardiovascular side-effects.[32] For acute mania, antipsychotics, lithium, or divalproex are indicated. The management of bipolar depression remains a

notable challenge[33] and controversy exists, particularly with regard to use of antidepressants[34] -- which despite limited evidence, remain commonly prescribed.[35] The medications used to treat mania carry variable propensity to induce weight gain as summarized in **Table 2**.

Table 2. Relative Propensity for Weight Gain by Medication

Severe	Moderate	Mild
Clozapine	Quetiapine	Lithium
Olanzapine	Risperidone	Other antipsychotics
Valproic acid derivatives		

Note: Variable weight gain within class of antipsychotics

Treatment may also produce significant changes in serum lipids. In one study of medication-naïve participants treated for one year with antipsychotics (haloperidol, olanzapine, or risperidone), participants experienced average triglyceride increases of 36.6 mg/dl (87.0 mg/dL to 123.6 mg/dL) or approximately 2 mmol/L.[36] Total cholesterol also increased by 22.2 mg/dL (174.7 mg/dL to 196.9 mg/dL).[36] Observational studies have found increases in triglycerides of 1 mmol/L to be associated with 18% increases in mortality in women and 8% in men, even after adjusting for other risk factors for vascular disease.[37] Changes in circulating cholesterol of 36 mg/dL have been associated with twice the risk of cardiovascular mortality.[38] Thus, the changes in lipid profile seen with medications may certainly convey clinically meaningful mortality risks. Antipsychotics and valproic acid are known to induce insulin resistance and increase the risk of developing diabetes mellitus.[39-41] It has also been suggested that shared genetic factors may increase risk for developing both bipolar disorder and vascular disease. Certain etiological pathways such as involving inflammation have also been potentially

implicated. These diverse potential causes are illustrated in **Figure 2**, which is adapted from Murray et al.[42]

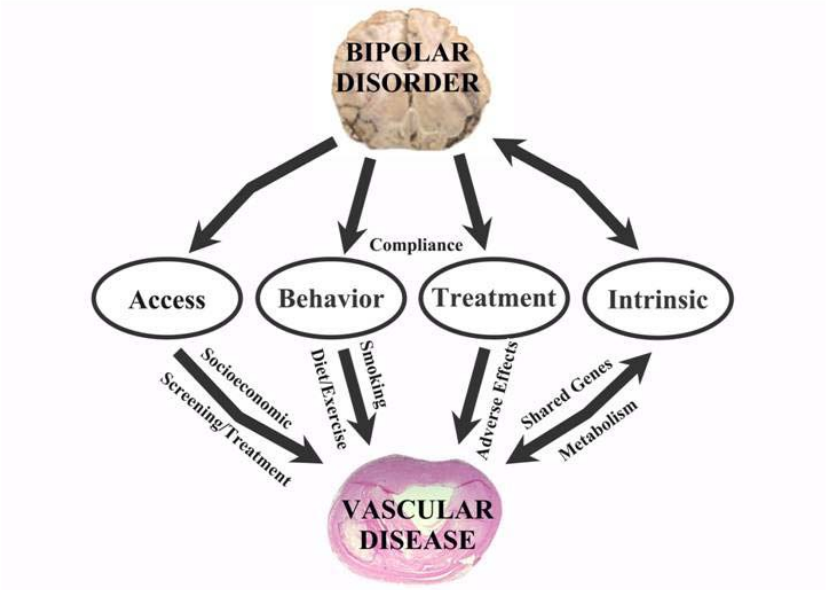

Figure 2. Potential Causes for Excess Vascular Disease in Bipolar Disorder.

To date, there exists insufficient evidence to estimate how much of the variance is explained by each of these potential contributing factors to the development of vascular disease in bipolar disorder. Identification of the most relevant mechanisms by which risk is mediated could assist in the development of targeted interventions to reduce risk.

Prevalence of risk factors for vascular disease in bipolar disorder

Much of the increased risk for vascular disease can likely be explained by the high prevalence of risk factors for vascular disease observed in bipolar disorder. Several vascular risk factors are more common in those with bipolar disorder than in the general population. These include obesity, hypertension, diabetes, and hyperlipidemia.

Obesity has been commonly associated with bipolar disorder. In one clinical sample of 644 patients with bipolar disorder, 79% of these patients were overweight or obese, and 5% of those were extremely obese compared to an estimated 60% in the general population.[43] Another sample of patients with bipolar disorder in Pennsylvania found that 45% of the patients were obese while another 29% were overweight.[44] In another study of participants with bipolar disorder and matched controls, cases with bipolar disorder weighed more, had a greater BMI, and had more fat content than the control subjects; however, estimated premorbid weights were not significantly different than those of the control subjects (and quantitatively less). This led the authors to conclude the weight gain results from the illness or treatment thereof.[45] A Norwegian study of 110 patients with bipolar disorder further found a greater risk of obesity than expected from the general population (24.9% vs. 14.1%) and a slightly greater risk than patients with schizophrenia (24.3%). The differences were even more pronounced when central obesity was measured (defined as a waist circumference of >102 cm in males or >88 cm in females). In the general population, only 16% met criteria for central obesity compared to 39.9% of individuals with schizophrenia and 54.2% with bipolar disorder.[46] Fiedorowicz et al. evaluated available data for body mass index in 161 patients with bipolar disorder and found more than 75% of the patients were overweight or obese and almost 50% were obese.[47]

Hypertension has been less consistently linked with bipolar disorder. Although two studies in the United States failed to find a greater than expected prevalence of hypertension in bipolar disorder,[44,48] other studies have found otherwise. An Iowa study by Yates and Wallace estimated the prevalence of hypertension at 14% in those with bipolar disorder compared to 5.6% in the control population and 5% in patients with unipolar depression.[49] In this study, a narrow definition of hypertension involved a diagnosis of hypertension, treatment with an antihypertensive, or systolic or diastolic blood pressure greater than 160/95 mm Hg. A Norwegian study estimated a prevalence

of hypertension of 61% in those with bipolar disorder versus 41% in the general population.[46] This study used a lower and more contemporary threshold with a systolic or diastolic pressure greater than or equal to 130/85 mm Hg. Johannessen et al. arguably conducted the definitive study to date. They compared 25,339 people with bipolar disorder to a control population of 113,698 and demonstrated an increased rate of incident hypertension among those with bipolar disorder relative to both the control population and individuals with schizophrenia. The incident rate ratio in this study was 1.3, suggesting those with bipolar disorder were 30% more likely to be newly diagnosed with hypertension than the general population.[50] The assessment of incidence rather than prevalence may mitigate some of the bias inherent to the study of medical co-morbidity in psychiatric populations. Admitting some inconsistencies, the data does support some increased risk of hypertension among those afflicted with bipolar disorder.

A relationship between bipolar disorder and diabetes was first entertained 90 years ago.[51,52] Contemporary clinical studies have substantiated this. One study found that, among inpatients, 9.9% of bipolar patients suffered from diabetes as compared to only 3.3% in the general population.[53] An older sample of 4,210 veterans also revealed a significantly greater prevalence of diabetes among bipolar patients, 17.2% versus 15.6%.[48] Additionally, 5.5% of 113 participants with bipolar disorder in Norway were found to have diabetes compared with 2.2% of the general Norwegian population.[46]

The presence of bipolar disorder appears to convey a greater risk of dyslipidemia. In one study, almost half of the patients (48%) with bipolar disorder were found to have hypertriglyceridemia or lipid-lowering treatment (metabolic syndrome criteria #2) compared to only 32% of the general population.[44] Among 77 patients with bipolar disorder with a recorded lipid profile, Fiedorowicz et al. found almost a third were diagnosed with hypertriglyceridemia although there was considerable potential for surveillance bias.[47] The most consistent findings with dyslipidemia appear to relate specifically to hypertriglyceridemia.

The metabolic syndrome can be conceptualized as a composite measure of many of these cardiovascular risk factors. The metabolic syndrome consists of several defining components: visceral obesity, hypertriglyceridemia, low HDL, hypertension, and insulin resistance. A review by Murray et al. suggested an overall prevalence ratio in bipolar disorder of 1.4 for United States studies and 1.8 for studies abroad. The lower prevalence ratio in the United States was hypothesized to be due to the greater general population prevalence of metabolic syndrome in the United States.[42]

The higher prevalence in traditional risk factors for vascular disease may explain the greater cardiovascular mortality seen in bipolar disorder. However, a final, and important, lingering question in many studies of death and bipolar disorder is whether excess mortality is related to an unidentified, inherent feature of mental illness or is mediated entirely through traditional risk factors for cardiovascular disease.

Limitations of existing data

Despite significant data indicating that there is an association between bipolar disorder and elevated risk for cardiovascular morbidity, there are still many questions that remain unanswered. Most of the evidence supporting a greater risk of cardiovascular mortality disorder is based on mortality studies of clinical (especially inpatient) samples of individuals with or without bipolar disorder. Studies have been limited in their ability to address selection bias, to identify a dose response relationship between illness and outcome, and to demonstrate temporality. Many of the studies collect participants from a population that consists solely of individuals who have been admitted to hospitals for their mental illness could also lead to selection bias. Inpatient samples are prone to selection or Berkson's bias[15] and the magnitude of such bias is not possible to estimate, even if unlikely to explain the findings altogether. Excluding patients with bipolar disorder who did not require hospital admission for mental illness may result in greater estimates of cardiovascular mortality. The identification of a dose-response relationship between illness and mortality could potentially assist in both circumventing selection

bias, but also providing additional evidence for causality. One way to mitigate such bias and to provide further evidence for a causal relationship[54] is to identify a dose response between mood and subsequent outcomes. Only a few studies, in major depression[55-60] and bipolar disorder,[61] have identified a dose-response relationship between illness and this cardiovascular mortality. Of those studies identifying dose-response, most[55-57,59] have simply assessed severity cross-sectionally rather than using longitudinal data and the only such study to do this specifically in bipolar disorder is presented later in Chapter 3. With an episodic course common to mood disorders, as previously illustrated in **Figure 1**, methods of dosing mood quantitatively using longitudinal data may better classify symptom burden as an exposure, though the requisite data are seldom available. Mood can also be "dosed" by the amount of time spent over the long-term course with clinically significant symptoms. **Figure 3** illustrates this concept. In the illustration, chronicity of illness can be dosed by the amount of time spent outside a specified range. Because measurements of mood are ordinal in nature, an area under the curve cannot conceivably be calculated. Herein, we refer to chronicity of clinically significant mood symptom as symptom burden. Prior prospective studies of symptom burden have found manic[61] but not depressive symptoms[60,61] associated with subsequent cardiovascular mortality. Whether or not there is a temporal association between affective illness and cardiovascular comorbidity is also unknown, as well as the nature of that association.

Vascular phenotyping methods have also been underutilized. There has been limited study of vascular function in mood disorders, with available research demonstrating significant impairments in vascular function or stiffness with depression and bipolar disorder in most[62-66] but not all studies.[67] These cross-sectional studies have focused on presence or absence of illness without dosing mood[64-66,68] apart from assessing duration of illness.[62] A dose-response relationship between symptom burden and vasculopathy, defined as the structural or functional evidence of vascular disease, has

not been studied and may be useful to delineate mechanisms by which course of illness may influence the development of vascular disease.

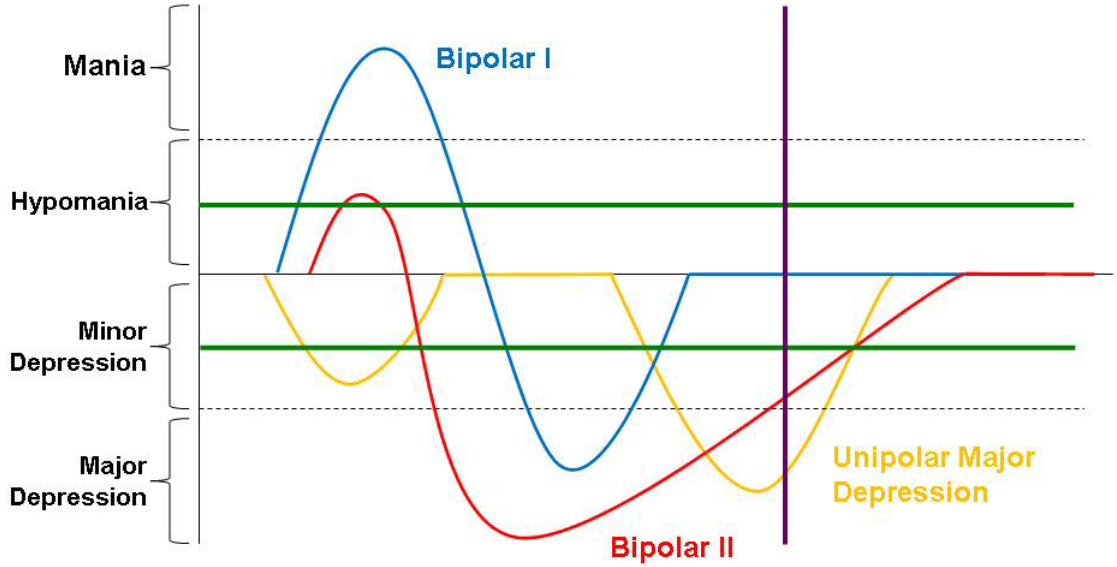

Figure 3. Conceptual Model for Dosing Mood. Dosing mood by the severity of illness at one point in time, as indicated by the vertical purple line, fails capture severity of illness over the long-term course. Mood can alternatively be dosed through ascertainment of symptom burden, defined as the amount of time with clinically significant mood symptoms, as indicated by symptoms exceeding the bounds of the horizontal green lines. Adapted from figure created by Tao Zhang.

CHAPTER II

THE PREVALENCE OF VASCULAR DISEASE AND RISK FACTORS IN A REPRESENTATIVE SAMPLE

Aims

To circumvent the selection bias inherent to studies of cardiovascular morbidity and mortality in bipolar disorder, cross-sectional data from a representative community sample was sought to estimate the prevalence, relative to the general population, of vascular disease and risk factors for vascular disease in bipolar disorder.[69]

Methods

Sample

The National Comorbidy Study – Replication (NSC-R) was conducted between February 2001 and April 2003 and involved a face-to-face household survey of adults (≥18 years of age) from a representative sample of the 48 contiguous United States. To reduce respondent burden, internal sub-sampling divided the interview into two parts. Part I focused on the diagnostic assessment of mental disorders, whereas Part II included additional information relevant to broader aims, including, but not limited to, the assessment of physical co-morbidity. All respondents completed Part I whereas Part II oversampled the original 9,282 NCS-R respondents to include all participants with diagnosable mental disorders.[70] Sample weightings adjust for differential probabilities of selection within households and for differences in intensity of recruitment effort. As a result of weighting, sample distributions closely match the population of the United States on sociodemographic variables. Thus, data from this sample allows for the assessment of risk for vascular disease in mental illness in a representative community sample. For this analysis, our sample was drawn from the 5,692 Part II NCS-R respondents, which included the requisite data on vascular disease and risk factors for

vascular disease. The final sample (N=3,688) included 101 individuals with bipolar I disorder, 243 individuals with bipolar II disorder, 1,573 individuals with major depressive disorder, and 1,771 individuals without mental illness.

For recruitment, participants were mailed a letter and brochure, followed by a face-to-face visit. Verbal informed consent was obtained by interviewers prior to beginning the interview. Trained interviewers were from the Institute for Social Research at the University of Michigan and received at least 7 days of study-specific training. Assistance to interviewers was provided from laptop computer-assisted software with timing flags, skip-logic, and consistency checks. A random sample of 10% of participants was recontacted by supervisors for quality control purposes. Participants were appropriately compensated for their time. The overall response rate was 70.9%. The Institutional Review Board (IRB) approved the protocol at Harvard Medical School in Boston, MA and the University of Michigan in Ann Arbor, MI. Further details of the study methods are available elsewhere.[70,71]

Diagnostic assessment

Diagnoses of mental disorders were made using the World Mental Health (WMH) version of the World Health Organization Composite International Diagnostic Interview (CIDI version 3.0). The CIDI is a fully structured assessment developed for trained non-clinician interviewers from diverse communities for the purpose of WMH surveys.[72] For the present analyses, mood disorder diagnoses considered include bipolar I disorder, bipolar II disorder, and major depressive disorder (MDD). The diagnosis of bipolar I disorder was made based on a lifetime history of mania and the diagnosis of bipolar II disorder was based on a lifetime history of hypomania without mania. Validity studies from the NCS-R have demonstrated good concordance between CIDI diagnoses and blind clinical diagnoses.[72-74]

Covariates

Sociodemographic characteristics including age, sex, employment, income, marital status, race/ethnicity, smoking, and urbanicity were obtained from self-report. Age was stratified into three groupings: less than 40 years, 40 to 59 years, or greater than or equal to 60 years. Age groupings were selected to facilitate comparison to contemporaneous data from the National Health and Nutrition Examination Survey (NHANES).[75,76] The ratio of family income to the census-based poverty income threshold was divided into four groups: 0 to 1.5 (low), 1.6 to 3 (low-average), 4 to 6 (high-average), or greater than 6 (high). Education level was grouped into four mutually exclusive categories: less than high school, high school graduate, some college, or college graduate or higher. Smoking status was classified as current, former, or never. Marital status was categorized as follows: married/cohabitating, previously married, or never married. Race was classified as Hispanic, Non-Hispanic Black, Other, and Non-Hispanic White. Employment was grouped into the following categories: currently working, homemaker, student, retired, or other. Urbanicity was obtained by linking location to data on the urban-rural continuum of counties according to standards of the United States Department of Agriculture and was categorized as major metropolitan counties, other urbanized counties, or rural counties. Family history of heart disease was based on self-report of any first degree relative with serious heart problems.

Outcomes

Chronic medical conditions were assessed on all Part II respondents. Participants were asked if they had ever had any stroke or heart attack at any time in their life. Part II respondents were further asked if a doctor or other health professional ever told them that they had heart disease, high blood pressure, and/or diabetes or high blood sugar. Obesity was defined as a body mass index greater than or equal to 30 kg/m^2 as calculated from self-reported height and weight. The primary outcome, co-morbid vascular disease was operationally defined as any self-report of heart attack, heart disease, or stroke.

Secondary outcomes included risk factors for vascular disease: high blood pressure, diabetes mellitus, and obesity.

Statistical Analysis

Cross-tabulations were used to estimate the frequency of sociodemographic and clinical variables. Logistic regression was applied to examine the relationship of mood disorders on dichotomous dependent variables (vascular disease and risk factors for vascular disease including obesity, high blood pressure and diabetes. Odds ratios (ORs) were calculated from the coefficients derived from logistic regression to estimate the likelihood of vascular disease or risk factors for vascular disease, after controlling for sociodemographic and clinical covariates. Individuals without mental disorders served as the reference group for all comparisons to the mutually exclusive, hierarchical mood disorders (mania, hypomania, major depression). Variances and 95% confidence intervals (CIs) of ORs were estimated using Taylor series linearization method using SUDAAN version 9. Statistical significance was based on 2-sided design-based tests evaluated at the 0.05 level of significance. Summary odds ratios of risk for vascular disease in those with mood disorder versus those without mood disorder stratified by gender were reported.

Results

The sociodemographic characteristics of those with mania, hypomania, MDD, or without mental disorders are detailed in **Table 3**. Individuals with mood disorders were more likely to be younger and female than those without mental disorders. Individuals with mania and hypomania were more likely to be low income and current smokers though were less likely to be married or cohabitating. Groups also did not differ on family history of heart disease. These sociodemographic variables served as covariates in subsequent logistic regression models.

Table 3. Sociodemographic Characteristics of NCS-R Subsample (n=3,688)

Variable	Category	Mania (n=101) %	Hypomania (n=243) %	MDD (n=1573) %	No MI (n=1,771) %
Sex	Male	39.8	44.7	37.2	47.9
	Female	60.2	55.3	62.8	52.1
Age	< 40 yrs	59.2	52.0	43.0	36.1
	40-59 yrs	37.1	41.3	43.9	34.7
	60 yrs	3.8	6.7	13.1	29.2
Urbanicity	Metropolitan	41.9	33.3	39.6	39.3
	Other Urban	41.6	30.1	29.1	27.2
	Rural	16.5	36.6	31.3	33.5
Income	Low	32.2	30.9	20.5	21.4
	Low-average	28.6	21.5	19.8	21.5
	High-average	25.6	30.6	33.6	31.9
	High	13.7	17.1	26.2	25.2
Smoking	Current	59.4	46.2	31.0	18.7
	Former	18.9	20.4	27.4	27.9
	Never	21.7	33.4	41.6	53.4
Marital Status	Married/Cohabiting	43.2	43.7	51.1	59.1
	Previous Married	20.5	25.8	25.8	20.0
	Never Married	36.3	30.5	23.2	21.0
Race/Ethnicity	Hispanic	16.4	11.5	9.2	11.8
	Non-Hispanic Black	15.1	16.9	8.0	13.9
	Other	3.8	5.1	4.4	3.4
	Non-Hispanic White	64.6	66.5	78.4	71.0
Employment	Other	21.7	24.6	12.8	7.3
	Working	62.6	64.8	70.9	62.9
	Student	4.6	2.4	2.0	3.0
	Homemaker	6.6	2.4	4.9	6.3
	Retired	4.5	5.8	9.4	20.6

Note: MDD=Major Depressive Disorder, MI=Mental Illness

The frequency of comorbid vascular disease and risk factors for vascular disease are reported for each mood disorder diagnosis by sex in **Table 4**. The odds ratios for

Table 4. Cardiovascular Disorders and Risk Factor Frequencies Stratified by Sex and Mood Disorder Diagnosis

Outcome	Male (n=1,429)							
	Mania		Hypomania		MDD		No MI	
	n=38		n=97		n=524		n=770	
	%	SE	%	SE	%	SE	%	SE
Vascular Disease	6.1	4.0	9.7	4.3	10.9	1.4	10.5	1.6
Obesity	34.1	9.5	27.8	6.5	28.7	2.1	26.5	2.4
High Blood Pressure	23.2	6.7	30.2	3.4	27.5	3.1	24.8	1.3
Diabetes	8.3	4.5	4.7	2.2	8.9	1.6	7.7	1.1
	Female (n=2,259)							
	Mania		Hypomania		MDD		No MI	
	n=63		n=146		n=1,049		n=1,001	
	%	SE	%	SE	%	SE	%	SE
Vascular Disease	10.8	4.1	12.1	2.3	7.4	1.0	7.6	0.9
Obesity	37.4	4.9	35.6	4.8	27.8	1.2	24.5	1.9
High Blood Pressure	18.4	4.5	24.8	4.1	23.3	1.3	23.5	1.6
Diabetes	11.0	2.8	11.4	2.1	6.4	0.8	8.0	1.1

each of these conditions after modeled in multivariate logistic regression are further reported in **Table 5**. When adjusted for age, urbanicity, income, education, smoking, marital status, race/ethnicity, employment, and family history of heart disease; the risk of vascular disease was elevated for women (OR 3.12, 95% C.I. 1.85-5.25) but not men (OR 1.70, 95% C.I. 0.61-4.77) with bipolar disorder (mania or hypomania). In parallel models, the risk of vascular disease was elevated for men (OR 1.90, 95% C.I. 1.23-2.95) but not women (OR 1.52, 95% C.I. 0.93-2.49) with major depression. After additionally controlling for the presence of obesity, high blood pressure, and diabetes in the full models, the risk remained elevated for women with bipolar disorder (OR 2.80, 95% C.I. 1.63-4.80) and men with MDD (OR 1.85, 95% C.I. 1.17-2.92). The greatest risk was

Table 5. Sex-specific Associations Between Mood Disorders and Vascular Diseases / Risk Factors

Mood Disorder	Male				
	aOR (95% CI) [1]				aOR (95% CI)[2]
	Vascular Disease[3]	Obesity	High BP	Diabetes	Vascular Disease[3]
Mania	0.90 (0.18-4.60)	1.70 (0.79-3.66)	1.28 (0.46-3.60)	1.40 (0.39-5.05)	0.91 (0.16-5.15)
Hypomania	2.05 (0.63-6.72)	1.18 (0.67-2.09)	2.22 (1.55-3.19)	0.78 (0.29-2.07)	1.89 (0.58-6.23)
MDD	1.90 (1.23-2.95)	1.16 (0.89-1.51)	1.52 (1.01-2.29)	1.49 (0.88-2.53)	1.85 (1.17-2.92)
Mania /Hypomania /MDD vs. No MI	1.87 (1.22-2.86)	1.18 (0.93-1.50)	1.59 (1.12-2.27)	1.40 (0.87-2.25)	1.80 (1.16-2.82)
No MI	Reference	Reference	Reference	Reference	Reference
	Female				
Mania	4.14 (1.42-12.02)	2.00 (1.20-3.34)	1.82 (0.86-3.84)	2.50 (1.17-5.33)	3.87 (1.42-10.56)
Hypomania	2.84 (1.59-5.06)	1.61 (0.93-2.78)	1.71 (1.05-2.77)	1.79 (1.06-3.04)	2.51 (1.35-4.66)
MDD	1.52 (0.93-2.49)	1.29 (1.01-1.65)	1.63 (1.23-2.15)	1.12 (0.71-1.76)	1.45 (0.87-2.42)
Mania /Hypomania /MDD vs. No MI	1.72 (1.12-2.66)	1.36 (1.06-1.75)	1.64 (1.28-2.11)	1.25 (0.83-1.89)	1.63 (1.04-2.55)
No MI	Reference	Reference	Reference	Reference	Reference

[1] Adjusted for demographics including age, urbanicity, income, education, smoking, marital status, race, employment & family history of heart disease

[2] Adjusted for demographics, obesity, high blood pressure and diabetes

[3] Vascular disease includes stroke, heart disease or heart attack

BP = Blood pressure, CI = Confidence interval, MDD = Major depressive disorder, MI = Mental illness

seen for women with a history of mania (OR 4.14 95% C.I. 1.42-12.02); even after additionally adjusted for obesity, high blood pressure, and diabetes (OR 3.87 95% CI 1.42-10.56). The odds ratios for vascular disease, obesity, high blood pressure, and

diabetes were qualitatively higher for women with mania and hypomania. When the interaction of sex and mood disorder on vascular disease was assessed within multiplicative models, no evidence of positive synergistic effects was found. Estimates by gender for those with bipolar disorder, however, had limited precision due to the low observed frequencies of vascular disease in each cell, for instance men with bipolar disorder. Pooling all individuals with mood disorders, odds ratios for vascular disease are similarly significant for men (OR 1.87, 95% C.I. 1.22-2.86) and women (OR 1.72, 95% C.I. 1.12-2.66) as illustrated in **Figure 4**.

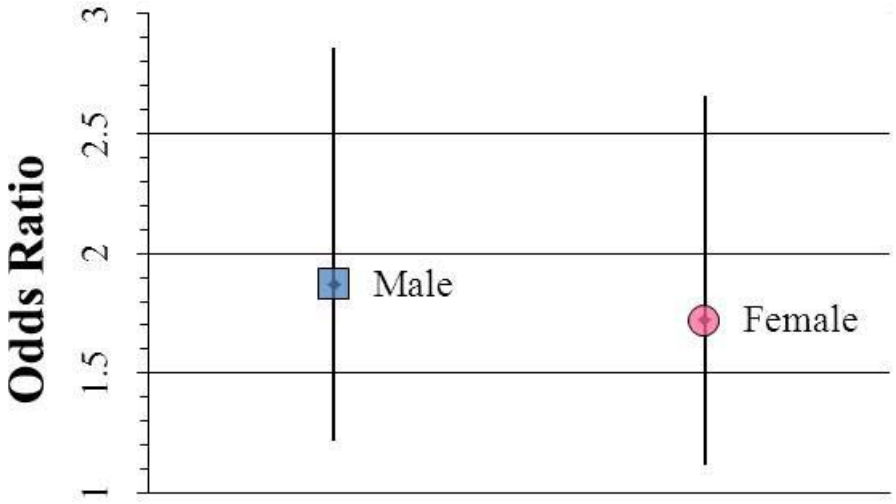

Figure 4. Odds Ratio by Gender for Vascular Disease in Mood Disorders.

Discussion

The results from this nationally representative sample of adults from the contiguous United States confirm that vascular disease and risk factors for vascular disease are more common among those with mood disorders. The greatest risk was seen

for women with bipolar disorder, particularly bipolar I disorder. These associations appeared independent of a number of sociodemographic and clinical variables and even the assessed traditional risk factors for vascular disease: diabetes mellitus, family history of heart disease, high blood pressure, obesity, and smoking.

Although a two-fold increase in heart disease among those with mood and anxiety disorders was found in the World Mental Health (WMH) surveys,[77] the relationship was not addressed independent of risk factors for vascular disease. A prior analysis from the NCS-R demonstrated a higher odds ratio for obesity with a lifetime diagnosis bipolar disorder (OR 1.47, 95% C.I. 1.12-1.93) compared to major depression (OR 1.21, 95% C.I. 1.09-1.35) with even greater differences by polarity for past year instead of lifetime diagnoses (OR 1.61 versus 1.09).[78] The associations between mood and anxiety disorders with obesity (ORs 1.2-1.5) were only significant for females in the WMH survey.[79,80] Our findings are consistent with and extend these prior findings on heart disease and risk factors from the WMH and obesity from the NCS-R. However, the somewhat lower magnitude associations from the current analysis relative to earlier analyses of the NCS-R and the WMH survey [77,79,80] are likely attributable to our inclusion of more covariates or our more broadly defined vascular disease variable, which included self-reported heart disease, heart attacks, and stroke. Our analysis was also unique in assessing whether vascular disease risk was independent of available vascular risk factors.

Numerous biologically plausible mechanisms may link vascular disease to mood disorders and could explain risk of vascular disease independent of traditional risk factors.[81] Potential biological links include altered immune function / inflammation,[66,82,83] autonomic nervous system dysfunction,[66,84] hypothalamic-pituitary-adrenal axis dysfunction,[85] pro-coagulant states,[86] and vascular dysfunction.[66] The directionality of any relationship between mood disorders and disturbed physiology is not

established and the associations could also result from common underlying genetic factors.[87]

The prevalence of vascular disease and risk factors for vascular disease in the NCS-R was comparable to data from other U.S. community and clinical studies. In this sample, obesity was present in 36% of those with bipolar I and 32% of those with bipolar II compared to data from U.S. clinical samples ranging from 32-50%.[43-45,47,88] The observed associations with high blood pressure and diabetes mellitus are also comparable to those from other population surveys including the Department of Veterans Affairs National Study [48] and NHANES.[76] In our study, a history of heart attack was reported by 3.2% of respondents, somewhat fewer than the 4.1% reported in NHANES,[89] although our sample of Part II respondents intentionally over-samples those with mental disorders who tended to be younger. The National Epidemiologic Survey on Alcohol and Related Conditions showed a stronger association between major depression and coronary heart disease (OR 2.05).[90]

Key limitations of the current study relate to the cross-sectional design and reliance on self-report. Self-report of height and weight may underestimate the prevalence of obesity.[91] Indeed, our estimates of obesity are lower than would be expected from published data for the same period from NHANES 2001-2002.[75] Despite this likely underestimation, the prevalence of obesity in subgroups with mood disorders remained markedly higher than expected. For instance, the prevalence of obesity for individuals 40-59 year of age with mania was 49% compared to the expected 34% from NHANES and the 33% observed among those without mental disorders. Differential misclassification of reported height and weight is possible although under-reporting of weight does not appear to differ in magnitude between depressed and non-depressed individuals.[92,93] The determination of vascular disease equivalents and risk factors represents another important limitation of the study. The small cell counts of vascular disease observed with less common conditions, such as bipolar subtypes, limits the

precision of odds ratio estimates and confidence intervals. Although of self-report of primary outcome is a concern, self-reporting of medically diagnosed vascular disease has acceptable validity[94-96] and has been applied in related research.[15,77,79,80,97-100] Those in treatment for mental disorders may still have had greater surveillance for metabolic and vascular conditions. This potential bias is mitigated though identification of mental disorders using the structured interview and instead of a sample already diagnosed or in treatment. Also, individuals with serious mental disorders are less likely to be screened for these conditions,[47,101] which also reduces the impact of this potential bias. Another key limitation relates to the cross-sectional study design, which is not suited to address temporality. In the analyses, we controlled for high blood pressure, diabetes mellitus, or obesity to ascertain whether the risk of vascular disease occurred independent of these traditional risk factors. These variables are considered categorically and without the presence of other established risk factors for vascular disease, such as those provided in a lipid profile. Subsequently, the possibility of residual confounding persists. The variables may alternatively be conceptualized as mediators and controlling for them could subsequently underestimate the magnitude of the association between mood disorders and vascular disease.

The NCS-R offers several advantages over prior studies of vascular disease and vascular risk factors in those with mood disorders. The sample was designed to be representative of the non-institutionalized population of the contiguous United States and the results are therefore readily generalizable. Prior clinical and community samples may not be representative of the general population with mental disorders, potentially exaggerating estimates on the prevalence of vascular co-morbidity. The NCS-R findings reduce the likelihood that the associations seen in prior studies can be merely dismissed due to selection or Berkson's bias. This may particularly apply to the relationship with obesity because body mass index was calculated from self-reported height and weight

and did not require a clinician diagnosis. Therefore, the nature of our sample and the findings observed reduce the likelihood the results are either spurious or biased.

Another notable strength of the study is the use of the structured CIDI instrument, a reliable and validated evaluation for mental disorders. The CIDI allows use of lifetime diagnoses, which are preferable for study of vascular disease, which presumably results from more long-term biobehavioral mechanisms. The size of the NCS-R dataset also allowed for stratification by sex and diagnosis, especially with more common outcomes.

Our overall findings strongly support prior studies reporting greater vascular disease with mental disorders and further identify a sub-group who appears to be at particular risk – women with bipolar disorder. The relationship between vascular disease and risk factors in individuals with mood disorders underscores the importance of screening and appropriate treatment for vascular disease and risk factors for vascular disease in these at-risk populations. Given that this risk cannot entirely be accounted for by sociodemographic and other clinical risk factors, including available risk factors for vascular disease, research into potential shared mechanisms between vascular disease and mood disorders is warranted.

CHAPTER III

DOSE RESPONSE BETWEEN MANIC MORBIDITY AND CARDIOVASCULAR MORTALITY

Aims

In this prospective cohort study, we sought to determine whether participants with bipolar I experience excess cardiovascular mortality relative to their bipolar II counterparts as previously reported by Angst et al.[21] Another objective of the study was to determine the influence of the burden of clinically significant symptoms and exposure to specific medications on cardiovascular mortality in bipolar disorder. We hypothesized that medication exposure and symptom burden would be associated with cardiovascular mortality.[61] This builds on recent work quantifying the chronicity of severe illness and its impact on outcomes related to though not limited to psychosocial disability[102,103] and suicide.[104]

Methods

The Collaborative Depression Study (CDS)

The National Institute of Mental Health CDS investigated the course, etiology, nosology, natural history, and prognosis of mood disorders, recognizing these heterogeneous but unreliably classified conditions as a major public health issue.[105,106] The five participating sites of the clinical studies component of the CDS included Massachusetts General Hospital and Harvard University in Boston, Massachusetts; Rush Presbyterian – St. Luke's Medical Center in Chicago, Illinois; the University of Iowa in Iowa City, Iowa; New York State Psychiatric Institute and Columbia University in New York, New York; and Washington University in St. Louis, Missiouri. From these centers, a total of 955 individuals with mood disorders were recruited from 1978-1981

and followed for up to 31 years. All participants provided informed consent to participate in the CDS study.

CDS sub-sample

From the CDS cohort of individuals with unipolar major depression and bipolar disorder, a total of 435 participants with bipolar disorder were identified. This diagnosis was based on baseline and available prospective data at the time of the analysis as later described. CDS participants were Caucasian, English speaking, and had knowledge of their biological parents. These inclusion criteria were selected because of the genetic hypotheses being tested.

Baseline assessments

Sociodemographic and clinical information were utilized from baseline data acquired from the Schedule for Affective Disorders and Schizophrenia[107] and the Personal History of Depressive Disorders. An initial diagnosis of bipolar I was defined from an intake Research Diagnostic Criteria (RDC) diagnoses of either bipolar I, schizoaffective manic (mainly affective), or schizoaffective depressed (mainly affective) with a history of mania.[108] The latter categories are equivalent to mania as currently defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). An initial diagnosis of bipolar II was based on this diagnosis from the intake RDC.[108] While the DSM-IV and RDC require similar symptoms for a diagnosis of hypomania, the DSM-IV sets a four-day syndrome duration for diagnosis while the RDC alternatively sets two days as the threshold for a probable and one week as the threshold for a definite diagnosis. Because of this, the more stringent, definite diagnosis of hypomania was used for our purposes. An initial diagnosis of unipolar major depression was based on intake RDC diagnosis of major depressive disorder or schizoaffective-disorder, depressed, mainly affective subtype and no prior mania. The latter category is analogous to DSM-IV-defined major depression.

Follow-up assessments

Severity of affective psychopathology was categorized over follow-up using Psychiatric Status Ratings (PSRs) using the Longitudinal Interval Follow-up Evaluation (LIFE), which was administered every six months in the first five years and annually thereafter.[109-111] The PSRs provided weekly ratings of symptom levels for each RDC syndrome[112] and identified the initiation and conclusion of manic or hypomanic episodes for all participants, even those with an initial diagnosis of unipolar major depression.[108] The PSRs have intraclass correlation coefficients of 0.9.[111]

Follow-up ratings from the PSRs facilitated diagnostic reclassification of participants. Participants with unipolar major depression on intake who subsequently developed hypomania or mania during follow-up were reclassified as bipolar II or bipolar I, respectively. Participants with a diagnosis of bipolar II at intake, who subsequently developed mania, were re-classified as bipolar I. To consistently utilize the most appropriate diagnoses, these prospective diagnoses were used for all analyses on the assumption that earlier syndromes were a manifestation of the same illness. For instance, if an individual with bipolar I first presents with a depressive syndrome only to later to manifest mania, recognition of the initial depression as a bipolar depression provides a more parsimonious explanation than assuming the development of a new condition. PSR ratings, which were collected for every week of prospective follow-up, also determined the morbidity of mood symptomatology experienced over time for each individual. A week of clinically significant affective symptoms was operationalized by utilizing a PSR cutoff score of >2/6, which requires at least obvious evidence of the disorder, on the major depression, schizoaffective depression, mania, or schizoaffective mania scales or a score of 3/3, definite criteria, for minor depression, intermittent depression, or hypomania. These thresholds are illustrated in **Table 6**. The burden of depressive morbidity was expressed as the proportion of weeks during follow-up with clinically significant depressive symptoms. The burden of manic/hypomanic morbidity was

Table 6: Psychiatric Status Rating (PSR) Scales from the Longitudinal Interval Follow-up Evaluation (LIFE)

Code	Status	Definition
Six-point weekly PSR scale for major syndromes		
1	Asymptomatic --Usual self	Return to "usual self" without any residual symptoms of the disorder
2	Residual -- Mild symptoms or impairment	One or more symptoms of disorder in no more than mild degree
3	Partial Remission -- Moderate symptoms or impairment	Less psychopathology than full criteria yet obvious evidence of the disorder with no more than moderate impairment
4	Marked -- Major symptoms or impairment	Major symptoms or impairment but does not meet definite RDC criteria
5	Definite Criteria -- Without	Meets RDC criteria but is without prominent psychotic symptoms or extreme impairment
6	Definite Criteria -- Severe: Prominent psychotic symptoms or extreme impairment	Meets RDC criteria with prominent psychotic symptoms or extreme functional impairment
Three-point weekly PSR scale for minor syndromes		
1	Asymptomatic	No evidence of previously met RDC criteria
2	Probable Criteria -- Mild	Minor manifestations of disorder that do not meet full criteria
3	Definite Criteria -- Severe	Meets definite RDC criteria for disorder

expressed as the proportion of weeks during follow up with any clinically significant hypomanic or manic symptoms.

Treatment exposure was recorded over follow-up and pooled into the following medication classes: first-generation antipsychotics, second-generation antipsychotics, carbamazepine, lamotrigine, lithium, valproic acid derivatives, monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), other antidepressants, and benzodiazepines. To mitigate selection bias secondary to varied durations of follow-up, exposure was quantified as the proportion of weeks treated at any dose. Assuming the proportions were similar during periods not in follow-up, proportions were used to estimate cumulative exposure with the available

data. In this non-experimental study, treatment was provided in the community and study investigators observed all treatment but did not direct it.

Primary Outcome

When a death occurred during the prospective follow-up, information on cause of death was acquired from family informants and death certificates. The individual's social security number was also used to access vital statistics records through the National Death Index or the Social Security Death Index. As a supplement to this process, mortality of participants lost to follow-up was assessed through the National Death Index.

Statistical Analyses

Bipolar I disorder and bipolar II disorder were contrasted on baseline demographics and cardiovascular risk factors available at intake. T-tests and chi-square tests were used for continuous and categorical variables, respectively. Differences in symptom burden by bipolar subtype (I vs. II) were compared using the Wilcoxon Rank Sum Test. Kaplan-Meier survival curves illustrated time to cardiovascular death. Survival time reflected the number of weeks from CDS intake until cardiovascular death. Participants were censored at the later of when lost to follow-up or the most recent vital statistics survey. Censoring was assumed to be independent of our primary outcome, cardiovascular mortality.

To facilitate the interpretation of results, proportions for exposure were multiplied by a factor of 10. The resultant hazard ratios therefore reflect the influence of a 10% increase in affective symptom burden for the variables for manic/hypomanic and depressive morbidity or a 10% difference in the proportion of time exposed to medications. Symptom morbidity and treatment exposure were missing for 8 participants (1.8%). Because of the low frequencies of exposure for some medication classes, some classes of medication would not likely produce stable estimates in survival analysis. A

threshold for medication exposure was therefore set to include only those medications for which at least 10% of participants were exposed greater than one-quarter of follow-up. This cut-off was selected prior to running analyses, but after viewing frequencies of exposure. The analysis assumed proportional hazards for the exposures of interest.

Cox proportional hazards regression compared survival by bipolar subtype while adjusting for gender and age at intake as a continuous variable. Cox proportional hazards regression allows for the inclusion of relevant confounders, including our exposures of interest: affective morbidity and treatment exposure. Cardiovascular risk factors were conceptualized as mediators of cardiovascular mortality and subsequently were not included in the primary analysis. The presence of cardiovascular risk factors prior to onset of affective disorder was not known as all participants were not recruited with onset of illness and the presence of risk factors was assessed at intake. Age was modeled as a time-dependent covariate to assess any non-linear age effects. Other variables were modeled as fixed, assuming proportional hazards was not violated.

Key assumptions underlying the initial analyses were tested in sensitivity analyses. Medication exposure and symptom burden were only assessed during follow-up. Because the majority of participants were recruited in a mood episode, these estimates may have been greater, and likely more variable, for those with shorter durations of follow-up. In a sensitivity analysis, participants lost to follow-up were censored with the earlier of the most recent vital statistics survey or three years after loss to follow-up. This timeline was based prior to analyses on review of outliers for duration lost to follow-up prior to cardiovascular mortality. This resulted in the additional censoring of three individuals who had died from cardiovascular disease, prior to death, leaving 30 cardiovascular deaths included for this analysis. Cardiovascular risk factors or medical co-morbidities that were assessed at study intake were also included into this model. These variables included: diabetes mellitus, hypertension, history of myocardial infarction, and heart valve abnormality. Other risk factors, such as smoking and

dyslipidemia, were not collected on intake and not known. Since smoking was not assessed at intake, we separately compared groups by smoking status as assessed by the Charlson comorbidity index, administered in 2003 (sub-sample N=108). Smoking was not assessed at any point for the remaining 327 participants and was not assessed earlier for the sub-sample of 108 participants. Selective attrition was further assessed.

Results

Baseline Characteristics

Participants in this sample were followed for a median of 20 (mean: 16.3; SD: 8.6) years and for up to twenty-five years. The demographic and clinical characteristics of bipolar I and bipolar II participants are summarized in **Table 7**. Participants with bipolar I were significantly less likely to be female, to have had a heart valve abnormality, or to have had a prior medical or surgical hospitalization. Participants with bipolar I were also more likely to have been recruited as an inpatient and had a slightly lower Global Assessment Scale at intake, suggesting greater psychopathological morbidity at intake. Psychopathological morbidity, expressed as affective symptom burden, was included as a covariate in subsequent analyses. Age at intake and age of affective illness onset did not significantly differ by bipolar subtype.

Cardiovascular Mortality by Bipolar Subtype

Thirty-three cardiovascular deaths were recorded: 24 among those with bipolar I disorder and 9 among those with bipolar II disorder. The differences in time to cardiovascular death by bipolar subtype are illustrated in **Figure 5**. Bipolar I was significantly associated with cardiovascular mortality (HR=2.35, 95% C.I. 1.04–5.33, p=0.04) when modeled in Cox Regression, adjusting for gender and age.

Participants with bipolar I spent a median of 16% (mean: 27; SD: 28) of follow-up weeks with clinically significant depressive symptomatology and a median of 4% (11; 17) of follow-up weeks with clinically significant manic/hypomanic symptomatology as previously defined. The bipolar II group spent a median of 31% (mean: 37; SD: 28) and

Table 7: Demographic and Clinical Characteristics from CDS Sample by Bipolar Subtype (N=435)

Demographic/Clinical Characteristics	Bipolar I	Bipolar II
	N=288	N=147
	# (%)	#(%)
Age, mean (median; SD)	36.7 (34; 13.1)	35.7 (31; 13.4)
Age of onset (median; SD)	23.1 (21; 9.2)	22.1 (20; 9.6)
Female [a]	154 (53%)	96 (65%)
Inpatient [b]	261 (91%)	98 (67%)
Marital Status [e]		
Married	92 (32%)	56 (38%)
Divorced/separated	61 (21%)	38 (26%)
Single	127 (44%)	51 (35%)
Widowed	8 (3%)	2 (1%)
Educational Level [e]		
Without diploma	30 (10%)	23 (16%)
High school graduate	73 (25%)	42 (29%)
Some college	105 (36%)	42 (29%)
College graduate	80 (28%)	40 (27%)
Income [e]		
Unknown	12 (4%)	6 (4%)
Less than $10,000	103 (36%)	45 (31%)
$10,000 to less than $22,000	97 (34%)	55 (37%)
$22,000 to less than $34,000	45 (15%)	20 (14%)
$34,000 or greater	31 (11%)	21 (14%)
Medical History [e]		
Diabetes Mellitus	14 (5%)	3 (2%)
Hypertension	37 (13%)	20 (14%)
Heart valve abnormality [c]	13 (5%)	14 (10%)
Myocardial Infarction	8 (3%)	3 (2%)
Medical/surgical hospitalization [d]	211 (76%)	129 (88%)
Co-Occurring Psychiatric Diagnoses [d]		
Alcohol abuse	90 (28%)	40 (27%)
Drug abuse	22 (8%)	18 (12%)
Generalized anxiety disorder	13 (5%)	7 (5%)
Obsessive-compulsive disorder	6 (2%)	4 (3%)
Panic disorder	9 (3%)	6 (4%)
Phobic disorder	11 (4%)	12 (8%)

Note: [a] χ^2=5.6, df=1, p<0.02; [b] χ^2=38.7, df=1, p<0.001;

[c] χ^2=12.0, df=1, p<0.001; [d] χ^2=3.9, df=1, p<0.05; [e] Assessed at intake

0.4% (1; 3) with depressive and manic/hypomanic symptomatology, respectively. Participants with bipolar I had significantly more manic (p<0.001) and less frequent depressive symptoms (p<0.001). When controlling for symptom burden, the difference between bipolar subtypes was no longer significant, whereas the proportion of time with clinically significant manic/hypomanic symptoms was.

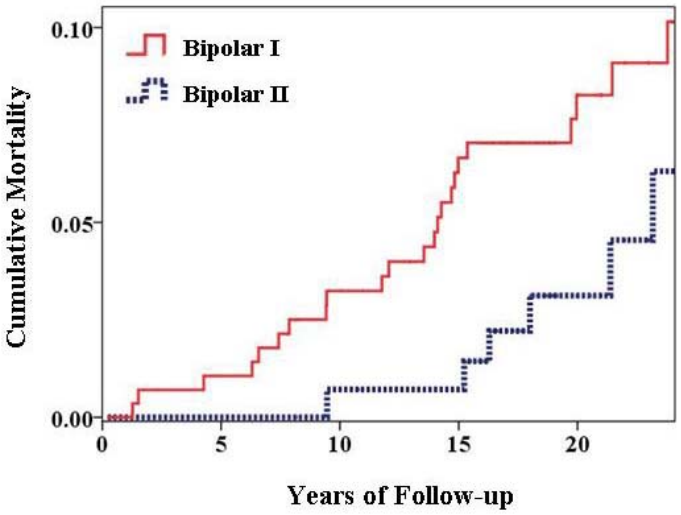

Figure 5. Cardiovascular Mortality in the CDS by Bipolar Subtype. Adapted from Fiedorowicz et al. *Psychosomatic Medicine* 2009.[61]

Medication Exposure and Affective Morbidity

Exposure was limited for some identified medication classes, particularly for those introduced late in the prospective cohort study. As expected, participants with bipolar I had greater medication exposure. Four medication classes: first-generation antipsychotics, lithium, TCAs, and SSRIs met our operationalized threshold for inclusion in the Cox regression analysis (10% of participants exposed for at least one-quarter of follow-up). Participants with bipolar I were more likely to be exposed to lithium and first generation antipsychotics a while those with bipolar II had greater exposure to

antidepressants. Exposures to second-generation antipsychotics, valproic acid derivatives, carbamazepine, lamotrigine, monoamine oxidase inhibitors, other antidepressants, and benzodiazepines were less common and/or circumscribed to a limited time period. SSRI exposure occurred later in follow-up with a median first exposure between years 12 and 13 of follow-up, at which point 12 cardiovascular deaths had already been recorded.

When modeled in Cox regression with age, gender, bipolar subtype, the proportion of weeks exposed to each of the four selected medication classes (first-generation antipsychotics, lithium, TCAs, and SSRIs), and the proportion of weeks with clinically significant depressive symptoms; the proportion of follow-up with clinically significant manic/hypomanic symptomatology was predictive (HR=1.30, 1.09–1.55, $p<0.01$) although bipolar subtype no longer predicted cardiovascular mortality (HR=1.85, 0.74-4.65, $p=0.19$). Exposure to first generation antipsychotics, lithium, and TCAs did not predict cardiovascular mortality. SSRI exposure appeared protective though was confined to the latter portion of follow-up. Depressive morbidity was not associated with cardiovascular mortality. The hazards ratio estimates for this primary model are detailed in **Table 8**.

TABLE 8: Hazards Ratio (HR) Estimates for Symptom Burden and Treatments on Cardiovascular Mortality in Bipolar Disorder

Variable	HR	95% C.I. HR
Age [a]	1.13	1.09 - 1.16
Male gender [b]	3.23	1.54 - 6.78
Bipolar I subtype	1.85	0.74 - 4.65
First-generation antipsychotics exposure	0.99	0.88 - 1.10
Lithium exposure	1.06	0.96 - 1.18
TCA exposure	0.87	0.74 - 1.03
SSRI exposure [b]	0.31	0.14 - 0.72
Manic symptom burden [b]	1.30	1.09 - 1.55
Depressive symptom burden	1.14	0.98 - 1.33

[a] $p<0.001$, [b] $p<0.01$

In reduced models, controlling for only age and sex to address the potential for overfitting, manic symptom burden remained significantly associated with cardiovascular mortality (HR=1.32, 95% C.I. 1.13-1.54, p=0.0004).

Sensitivity Analyses

Those lost to follow-up within the first year tended to have a greater percentage of follow-up with clinically significant manic/hypomanic symptoms (median of 2.5% versus 1.6%) though none died from cardiovascular causes. When those lost to follow-up in the first year are removed from the analysis, the relationship between manic/hypomanic symptom burden and cardiovascular mortality is only strengthened. For those followed actively through 2003, smoking was not associated with manic/hypomanic symptom burden (t=-1.1, df=106, p=0.3) or bipolar subtype (χ^2=0.8, df=1, p=0.3).

Because assessment of manic symptom burden was limited to the period of prospective follow-up, participants in the sensitivity analysis were censored if mortality was not assessed within three years of loss to follow-up. We additionally included available cardiovascular risk factors at baseline in this expanded model. With a dependent variable of time-to-cardiovascular mortality, the sensitivity analysis model included independent variables for a linear effect of age, sex, hypertension, history of myocardial infarction, heart valve abnormality, and diabetes mellitus, and the proportion of weeks with clinically significant manic/hypomanic symptoms. When modeled as such in Cox regression, manic/hypomanic symptomatology (HR=1.34, 95% C.I. 1.10–1.63, p=0.004) remained associated with cardiovascular mortality. A history of myocardial infarction and heart valve abnormality were also significantly associated as expected.

Discussion

In this prospective cohort study, manic/hypomanic symptom burden independently predicted cardiovascular mortality and largely explained the increased risk for cardiovascular mortality in bipolar I relative to the bipolar II subtype. While a number of studies have established an elevated risk for cardiovascular mortality with

bipolar disorder,[17,18,20-23,113,114] only one prior study assessed risk by bipolar subtype though did not assess the influence of exposure to specific medications or affective symptom burden.[21] Consistent with this prior work, we found a greater risk of cardiovascular mortality in participants with bipolar I than bipolar II. Apart from SSRI exposure, medication exposure did not appear to be related to cardiovascular mortality. While SSRI exposure appeared protective, the late exposure window and the magnitude of the estimated effect are suspicious for survivor bias. Surprisingly, manic/hypomanic but not depressive symptoms were associated with subsequent cardiovascular mortality and appeared to explain the observed differences between the bipolar subtypes.

This analysis has several important limitations. Some participants were lost to follow-up prior to the assessment of cardiovascular mortality. This loss to follow-up limits our ability to assess relevant exposures in the period prior to outcome for all participants. To mitigate this risk without losing focus on cumulative exposure, we utilized proportions of weeks exposed during follow-up for these variables. This assumes that similar levels of symptom burden are present during periods not in follow-up. These symptom burden measures have demonstrated some stability over long-term follow-up for individuals with bipolar disorder and major depression.[115,116] We also censored participants after lost to follow-up for greater than three years prior to mortality assessment in a sensitivity analysis. Our measures of medication exposure and affective symptom burden only infer cumulative lifetime exposure and assume the proportions observed during follow-up are representative of periods where participants were not followed prospectively. With many participants recruited during acute episodes, this limitation may overestimate the symptom burden and medication exposure for those lost to follow-up early, creating the potential for differential misclassification. Exclusion of those lost to follow-up within the first year did not alter our results. Limited observed exposure to some medication classes impeded a more refined medication exposure analysis. Our analysis of treatment exposure was therefore limited to first-generation

antipsychotics, lithium, and TCAs, yet participants were also taking other agents, the influence of which was not assessed. In this observational study, treatment was not randomly assigned and therefore treatment exposure could be confounded by a variety of factors, including but not limited to severity of illness and general health-seeking behaviors. Our assessment of baseline cardiovascular risk was limited by available data, with dyslipidemia, obesity, and tobacco notably absent. Prior studies of cardiovascular mortality in bipolar disorder also lacked dyslipidemia or smoking.[18,20-24,113,117] Our primary outcome, cardiovascular mortality, was observed in 33 participants (30 after censoring in the sensitivity analysis), limiting power. Nonetheless, we detected a robust and significant association between manic/hypomanic symptom burden and cardiovascular mortality. The expanded models risk overfitting the data, however, the findings generally reflected those of both our primary analysis and reduced models. The results from our Caucasian sample may additionally not generalize to other populations.

Despite these limitations, the CDS provided an exceptionally rigorous assessment of diagnosis, affective morbidity, and treatment over follow-up. Prior studies of cardiovascular mortality in bipolar disorder have relied on diagnostic data from medical records or registries, which may be less reliable than structured interviews at intake with ongoing assessment.[18,20,22-24,117] The use of prospective diagnoses also reduced the risk of diagnostic misclassification. Detailed ascertainment of affective morbidity revealed that differences in mortality by diagnostic subtype reflected the burden of manic/hypomanic rather than depressive symptomatology. Our estimates of affective morbidity were somewhat lower than prior analyses[109,110] due to exclusion of subsyndromal symptoms. The reported impact of manic/hypomanic symptoms could be mediated by physiological mechanisms intrinsic to the disease process, reflect shared genes conveying risk, or result from associated health behaviors. It is also possible that the association with mania is confounded by other variables, including unmeasured exposures or treatments.

SSRI exposure appeared to have a protective effect on cardiovascular mortality in this cohort. Fluoxetine was first introduced to the U.S. market in 1988. Of those exposed to SSRIs, first exposure occurred at a median of just under 13 years of follow-up. Thus, the apparent protective effect of SSRIs may be exaggerated by or even entirely reflect a survivor bias. Nonetheless, several properties of SSRIs, including inherent anti-platelet effects,[118] have been proposed to potentially reduce cardiovascular risk.[119] Given the limitations reported herein, however, definitive conclusions cannot be drawn regarding any protective benefit of SSRIs. The more limited and later exposure for second generation antipsychotics impeded assessment of associated risk, which based on their known impact on vascular risk factors, would have been worthwhile. The relevant exposure window for the long-term vascular side-effects of all medications studied is not known and alternative designs, such as using treatment intervals as the unit of analysis, may have been better suited to detecting medication effects. With medication use determined from clinical interview and not administrative or billing data, however, it would have been difficult to discern whether cardiovascular deaths occurred within or outside of a treatment interval. The current design, however, did facilitate the dosing of bipolar disorder severity based on the chronicity of clinically significant mood symptoms.

Bipolar disorder is a serious, potentially treatable medical condition with considerable morbidity[103,110,120-128] and mortality.[104,129,130] Our study extends a prior finding of greater cardiovascular mortality with the bipolar I subtype as relating to a previously unreported association between manic/hypomanic symptom burden and cardiovascular mortality. These findings warrant study of pathophysiological links between manic/hypomanic syndromes and cardiovascular morbidity.

CHAPTER IV

DO SYMPTOM BURDEN OR TREATMENT IMPACT VASCULOPATHY?

Aims

We sought to ascertain whether lifetime symptom burden or medication exposure are associated with vascular dysfunction in a sample with mood disorders whose phenomenological and treatment histories were rigorously assessed over up to 30 years through participation in the CDS. Based on prior findings with cardiovascular mortality in this sample,[61] we hypothesized that manic, not depressive, symptom burden would be associated with worse vascular function.[131] We further hypothesized that treatment with second generation antipsychotics and valproic acid derivatives would be associated with worse vascular function.[131]

Methods

CDS sub-sample

The CDS, as previously described in Chapter III, was a prospective cohort of individuals followed for up to 31 years to test hypotheses related to the nosology, phenomenology, and etiology of mood disorders.[105] The sample included Caucasian (genetic hypotheses), English-speaking participants, who had knowledge of their biological parents, and provided written informed consent. We recruited individuals who completed the CDS study at two of five CDS sites and resided near Iowa City. Participants with a history of diabetes, heart disease, hyperlipidemia, or hypertension at CDS intake were excluded. We also excluded individuals more than 80 years of age. Fifty-nine former participants from The University of Iowa in Iowa City, IA and 7 former participants from Washington University in St. Louis, MO, representing all of those meeting inclusion criteria were contacted, of whom 44 (75%) were female. Two of the male former participants had died in the interval. Recruitment procedures were approved by the respective Institutional Review Boards.

Assessments from CDS

On intake into the CDS, participants underwent interviews for the Schedule for Affective Disorders and Schizophrenia[107] and the Personal History of Depressive Disorders. Follow-up assessments categorized severity of affective psychopathology from PSRs using the LIFE, administered every six months in the first five years and annually thereafter.[109-111] The PSRs provided weekly ratings of symptom levels for each Research Diagnostic Criteria syndrome[112] as previously described[108] and discussed in Chapter III. Intake and follow-up ratings facilitated rigorous ascertainment of mood disorder diagnosis using established methods.[108,132]

PSRs were utilized to estimate affective morbidity. Using previously published methods (see also Chapter III),[61] a week of clinically significant affective symptoms was defined as a PSR cutoff score of > 2/6 on the major depression, schizoaffective depression scale, mania, or schizoaffective mania scales or a score of 3/3 for minor depression, intermittent depression, or hypomania. Burden of clinically significant depressive or manic/hypomanic morbidity was expressed as the proportion of weeks exceeding these thresholds for the respective syndromes. These measures have demonstrated stability over long-term follow-up for bipolar disorder and major depression.[115,116] Medication exposure was recorded during follow-up and included the following classes of medications: carbamazepine, first-generation antipsychotics, lamotrigine, lithium, second-generation antipsychotics, valproic acid derivatives, monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other antidepressants.[61] These classes were pooled into two broad medication classes: mood stabilizers/antipsychotics (carbamazepine, first-generation antipsychotics, lamotrigine, lithium, second-generation antipsychotics, valproic acid derivatives) and antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants,

selective serotonin reuptake inhibitors, other antidepressants). In this observational study, investigators observed but did not assign treatment.

Chart Review

Weight or other metabolic assessments were not obtained at baseline through the CDS. We systematically reviewed the medical records within two years of CDS intake of all participants to abstract height, weight, total cholesterol, blood pressure, and heart rate.

Metabolic and Vascular Assessments

Fasting for 12 hours and smoking cessation for 2 hours prior to assessment was verified by direct questioning. A research nurse measured vital signs, height, weight, waist circumference, and obtained a blood sample. The principal investigator and study physician took a medical and psychiatric history and performed a physical examination.

Vascular function was assessed using arterial tonometry (pulse wave analysis, pulse wave velocity) and conduit vessel function by trained staff blinded to diagnosis, current medications, and any CDS data. *A priori* established primary outcomes were flow-mediated dilation (FMD) and nitroglycerin (NTG)-mediated vasodilation of the brachial artery. FMD is an endothelium-dependent assessment of conduit vessel function, while NTG-mediated vasodilation provides an endothelium-independent measure of conduit vessel function. A trained sonographer assessed FMD and NTG-mediated vasodilation non-invasively by ultrasound measurement of brachial artery diameter using established methods[133] with a 10 MHz linear array transducer (Biosound Esaote AU5). These measures were selected as primary outcomes because they are the best studied and validated non-invasive measures of vascular function. However, they are seldom used clinically due to cost and the need for highly trained operators.[134] The brachial artery was imaged in a longitudinal section above the antecubital fossa. Baseline images of Bessel diameter and Doppler velocities were recorded. FMD was assessed one minute after release of an occluding forearm cuff that had been inflated to 50 mgHg

above systolic pressure for five minutes. After ten minutes of restoration of baseline flow and diameter, 400 mcg of NTG was administered by sublingual spray. NTG-mediated vasodilation was assessed four minutes later. Imagines representing the assessment of NTG-mediated vasodilation are illustrated in **Figure 6**. These imagine methods are analogous to the aforementioned methods for the assessment of FMD.

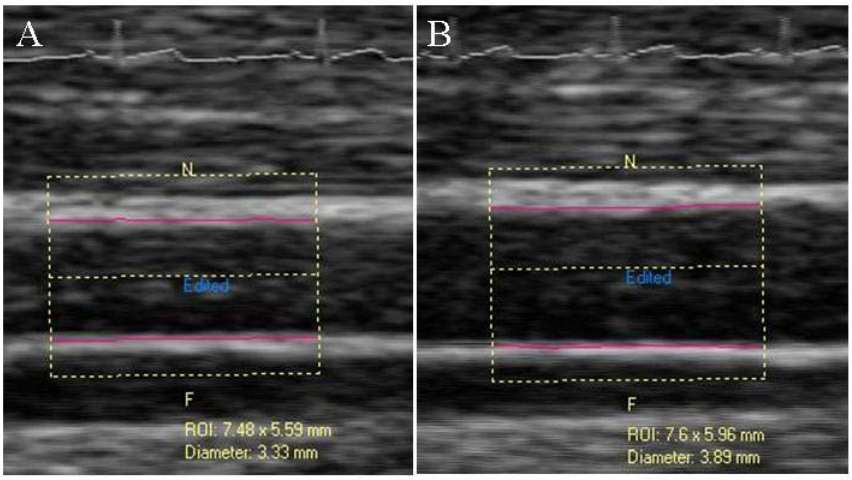

Figure 6. Conduit Vessel Images Before and After NTG-mediated Vasodilation. The left image (A) demonstrates the brachial artery diameter (3.33 mm) at baseline. The right image (B) illustrates the brachial artery diameter (3.89 mm) four minutes after receiving 400 mcg of sublingual nitroglycerin. This represents a 16.8% increase in diameter. Images were analyzed using Brachial Analyzer for Research, Version 5.0.3.

Secondary outcomes involved measures of arterial stiffness. Increased vascular stiffness translates into accelerated return of peripheral pulse waves to the aorta, leading to increases in augmentation pressure, augmentation index, and overall aortic systolic pressure. The four secondary outcomes were pulse wave velocity, aortic augmentation pressure, augmentation index (adjusted for heart rate of 75), and systolic aortic pressure. These measures were obtained using the Sphygmocor arterial tonometry system,[135] which

measures peripheral arterial pulse wave form and timing. An example of how these measures may be derived from a radial artery pulse wave form is shown in **Figure 7**. To measure pulse wave velocity, the pressure pulse waveform was recorded simultaneously with an electrocardiogram signal, which provides an R-wave timing reference. Recordings were performed at the carotid and femoral artery sites to measure velocity in a path that includes the aorta. Information from the peripheral pressure pulse waveform and the systolic and diastolic brachial artery pressures were used to derive central aortic pressure waveform and a range of central indices of ventricular-vascular interaction. The blood pressure pulse waveform is dependent on the stiffness of the artery along which the pulse if traveling.

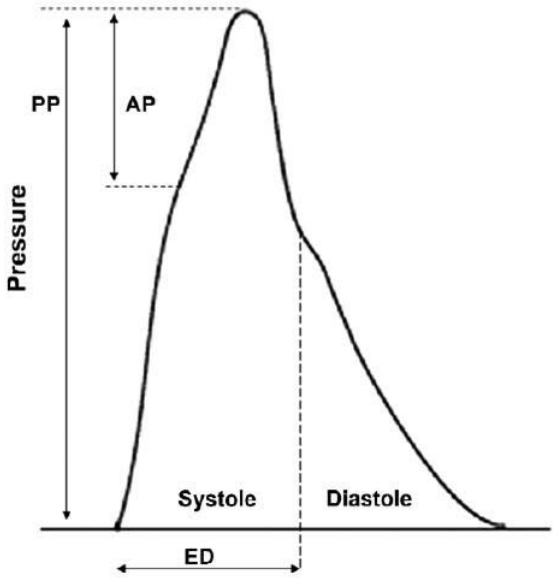

Figure 7. Dimensions of Peripheral Pulse Wave Form. Measurement of the pulse wave form allows for the measurement augmentation pressure (AP), which when compared to pulse pressure allows for the calculation of augmentation index and other measures. Augmentation index provides an estimate of the stiffness in the arterial system. Figure adapted from Crilly M et al. *Vasc Med* 2007.[136]

Exploratory outcomes included cardiovascular risk factors such as body mass index (BMI), waist circumference, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting triglycerides (total, LDL, very low density lipoprotein (VLDL)), apolipoprotein B, brachial (clinic) arterial pressure, insulin resistance (calculated from fasting glucose and insulin by homeostatic model assessment for insulin resistance (HOMA-IR)[137]), highly sensitive C-reactive protein, and interleukin-6.

Statistical Analyses

All analyses were conducted in SAS 9.2. Descriptive statistics were tabulated on a variety of demographic and clinical variables, which were compared to that of the all site CDS sample of those who completed at least 24 years of follow-up (N=362) using chi-square and t-tests tests for categorical and continuous variables, respectively.

The proportion of weeks with clinically significant hypomanic/manic and minor/major depressive symptoms during follow-up served to measure symptom burden. Given overlapping metabolic adverse effects and to minimize risk of Type I error on multiple comparisons, treatment exposures were pooled into two broad classes: mood stabilizers/antipsychotics and antidepressants. Analyses of more refined medication classes followed any significant findings. Given the infrequent use of carbamazepine and lamotrigine over long-term follow-up, these agents were not included in follow-up analyses for mood stabilizer / antipsychotic exposure though exposure to these agents was included in the pooled measure. Individuals on combinations of medications were considered exposed if any one of those medications belonged to an exposure group of interest. For instance, someone exposed to valproic acid and an antipsychotic for the same year of follow-up would record 52 weeks of exposure to this class of agents during this time. In this small sample, exposures of interest were modeled as the logit transformation of the proportion of time exposed to minimize the impact of outliers and to maximize the likelihood that residuals would be normally distributed. Linear

regression models were applied to examine the associations between symptom burden and treatment exposure on vascular function (dependent variable), controlling for age, gender, and tobacco exposure in pack*years. Symptom burden and medication exposure variables were modeled separately to mitigate multicollinearity (symptom burden and respective treatments were highly correlated in a small sample) and avoid overfitting. Linear regression models followed the following format:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \varepsilon$$

where Y represents our dependent outcome variable (a vascular function measure), X_1 is age (linear effect), X_2 is gender, and X_3 is tobacco exposure in pack*years. In symptom burden models, X_4 is proportion of follow-up with clinically significant depressive symptoms and X_5 is the proportion of follow-up with clinically significant manic or hypomanic symptoms. In the treatment models, X_4 is proportion of follow-up treated with antidepressants and X_5 is the proportion of follow-up treated with antipsychotics or mood stabilizers. To identify overfitting, sensitivity analyses using reduced models, including only age with symptom burden or treatment exposure variables, were created for any models producing significant results.

Exploratory analyses investigated the relationship between our exposures of interest (symptom burden and medication exposure) and potential physiological mediators: body fat percentage, BMI, waist circumference, brachial systolic blood pressure, laboratory measures, and HOMA-IR. Any variables significantly associated with exposures of interest (symptom burden and treatment exposure) were added to regression models in which exposures of interest were significantly associated with primary or secondary (vascular function) outcomes. The reduction in R^2 for the exposure of interest after inclusion of the potential physiological mediator was used to estimate possible impact. Mediation was further explored in a sub-sample of participants with available data from chart abstraction for changes in relevant mediators over CDS follow-up.

Results

Baseline Characteristics

A total of 35 participants (33 from the University of Iowa and 2 from Washington University) from two sites of the CDS consented for a cross-sectional vascular and metabolic assessment at the University of Iowa. Participants had been followed for a mean (SD) of 26.8 (1.2), median of 27, at least 24 and up to 30 years in the CDS. Demographic and characteristics of the sample are outlined in **Table 9**. The mean (SD) age of participants was 61(8) (range 50 to 76), 83% were female, and 57% had a diagnosis of bipolar disorder. The mean (SD) body mass index was 30 (6) and 63% had ever smoked tobacco. Participants significantly differed from others in the full CDS sample only regarding gender (χ^2=5.04, df=1, p=0.03) though did not significantly differ from those approached to participate.

FMD data could not be interpreted due to motion for one participant. Pulse wave velocity could not be obtained on four participants. Augmentation index could not be calculated to a heart rate of 75 due to unusually low resting heart rates for two participants. Because of this missing data, the total number of participants included in the analyses reported herein varies.

Depressive symptom burden was highly correlated with cumulative exposure to antidepressants (r=0.86, p<0.0001) as was manic symptom burden with cumulative exposure to mood stabilizers and antipsychotics (r=0.72, p<0.0001). For this reason, in this small sample, symptom burden and treatment variables were separately modeled. There was a moderate negative correlation between manic and depressive symptom burden (r=-0.47, p<0.004).

Symptom Burden and Vascular Function

Table 10 presents results of symptom burden and treatment exposure models on primary outcome measures. In multivariable linear regression, controlling for age,

Table 9. Characteristics of Sample (N=35)

	Mean (SD)
Age	61 (8)
Percent of time with clinically significant symptoms	
Depressive	30.0 (26.6)%
Manic/hypomanic (if bipolar)	7.1 (19.9)%
Body Mass Index (kg/m2)	29.8 (6.2)
Waist circumference (cm)	100.2 (15.4)
FMD diameter % change	4.6 (4.3)
NTG-mediated diameter % change	11.0 (5.4)
Augmentation pressure (mmHg)	14.9 (8.0)
Augmentation index adjusted for heart rate of 75	25.6 (9.2)
Systolic aortic pressure (mmHg)	122 (17)
Pulse wave velocity (m/s)	10.8 (3.8)
Triglycerides (mg/dL)	122.2 (91.6)
LDL-cholesterol (mg/dL)	121.6 (27.9)
HDL-cholesterol (mg/dL)	55.1 (12.5)
Glucose (mg/dL)	100.5 (16.6)
	# (%)
Female sex[†]	29 (83%)
Unipolar major depression	15 (43%)
Bipolar disorder	20 (57%)
Bipolar I	14 (40%)
Bipolar II	6 (17%)
History of tobacco use	22 (63%)
Medication treatment (any history of)	
First generation antipsychotics	25 (71%)
Second generation antipsychotics	11 (31%)
Valproic acid derivatives	13 (37%)
Lithium	22 (63%)
Carbamazepine	7 (20%)
Lamotrigine	3 (9%)
Antidepressants	31 (89%)

[†] Significantly higher than expected from the CDS at 24 years follow-up.

gender, and tobacco exposure, manic symptom burden was associated with lower flow-mediated dilation (t=-2.21, partial R^2=0.15, p=0.035). This would represent an absolute reduction of 2.2% (0.52 SD) in FMD (baseline=4.6%) across the interquartile range of

those with bipolar disorder (0.6 to 5.6% manic/hypomanic symptom burden). Using data from the entire CDS sample, this would represent an absolute difference of 2.3% dilation (0.54 SD) on FMD (or about a 50% relative change in FMD) between those with 0.4% and 4% manic/hypomanic symptom burden, the previously reported median for bipolar II and bipolar I respectively [61]. Manic symptom burden was not associated with NTG-mediated vasodilation. Depressive symptom burden was not associated with any of the tested measures as reported. Symptom burden measures were not associated with any of the secondary outcomes as shown in **Table 11**. Exploratory analyses associated manic symptom burden with hypertriglyceridemia (t=2.12, partial R^2=0.13, p=0.043), but not specifically with LDL-triglycerides or VLDL-triglycerides. Manic symptom burden was also associated with higher BMI (t=2.55, partial R^2=0.18, p=0.016), waist circumference (t=2.79, partial R^2=0.21, p=0.009), and HOMA-IR (t=2.94, partial R^2=0.23, p=0.006). Depressive symptom burden was associated with a higher heart rate (t=2.11, partial R^2=0.13, p=0.044). However, in the 28 participants with available data, manic symptom burden was not correlated with change in BMI nor was depressive symptom burden with change in heart rate.

Medication Exposure and Vascular Function

As noted above, antipsychotic/mood stabilizer and antidepressant exposure were not associated with FMD or NTG-mediated vasodilation. Treatment exposure models for arterial stiffness outcomes are reported in **Table 12**. Cumulative exposure to antipsychotics and mood stabilizers were, however, associated with arterial stiffness as evidenced by elevated aortic systolic augmentation pressure (t=2.66, partial R^2=0.20, p=0.013) and estimated aortic systolic blood pressure (t=2.37, partial R^2=0.16, p=0.025). As evidenced in the table, first generation antipsychotics were the only medication class significantly associated with the aforementioned findings. From these models, an increase of 5.8 mmHg (0.73 SD) in augmentation pressure and 16.8 mmHg (1.00 SD) in

aortic systolic blood pressure was observed across the interquartile range (3 to 44% exposure) of those exposed to first generation antipsychotics.

Table 10. Multivariate Linear Regression Models for Symptom Burden and Treatment on Primary Outcomes

	Beta	SE	t	*p*
Dependent Variable = FMD (N=34)				
Symptom Burden Model				
Depressive symptom burden	-0.576	0.385	-1.50	0.15
Hypomanic/manic symptom burden	-0.993	0.449	-2.21	*0.035**
Treatment Model				
Antidepressant exposure	-0.221	0.276	-0.80	0.43
Mood stabilizer/antipsychotic exposure	-0.225	0.173	-1.31	0.20
Dependent Variable = NTG-mediated dilation (N=35)				
Symptom Burden Model				
Depressive symptom burden	0.808	0.465	1.74	0.09
Hypomanic/manic symptom burden	0.308	0.536	0.57	0.57
Treatment Model				
Antidepressant exposure	0.411	0.320	1.29	0.21
Mood stabilizer/antipsychotic exposure	-0.111	0.204	-0.54	0.59

Note: All models controlled for age, gender, and tobacco exposure (pack*years)

* $p < 0.05$. Coded such that greater hypomanic/symptoms was associated with poorer endothelial function.

FMD = flow-mediated dilation, NTG = nitroglycerin

In exploratory analyses, first generation antipsychotics were significantly associated with elevated peripheral brachial systolic arterial pressure (t=3.41, partial R^2=0.28, p=0.002). Second generation antipsychotics were associated with insulin resistance (t=2.16, partial R^2=0.13, p=0.039) and hypertriglyceridemia (t=3.11, partial R^2=0.24, p=0.004). Exposure to valproic acid derivatives was associated with insulin resistance (t=2.28, partial R^2=0.15, p=0.030), hypertriglyceridemia (t=2.96, partial R^2=0.23, p=0.006), and low HDL-cholesterol (t=-4.33, partial R^2=0.38, p=0.0002). For

second generation antipsychotics and valproic acid derivatives, similarly significant results were observed for VLDL-triglycerides as total triglycerides, but LDL-triglycerides were not related to exposure. In the subset of 28 individuals with available data from

Table 11. Multivariate Linear Regression Models for Symptom Burden on Arterial Stiffness Measures

	Beta	SE	t	*p*
Dependent Variable = Augmentation Pressure (N=35)				
Symptom Burden Model				
Depressive symptom burden	-0.418	0.782	-0.54	0.60
Hypomanic/manic symptom burden	-0.384	0.900	-0.43	0.67
Dependent Variable = Augmentation Index adjusted for heart rate of 75 (N=33)				
Symptom Burden Model				
Depressive symptom burden	0.955	1.080	0.88	0.38
Hypomanic/manic symptom burden	0.526	1.000	0.53	0.60
Dependent Variable = Systolic Aortic Pressure (N=35)				
Symptom Burden Model				
Depressive symptom burden	-0.144	1.653	-0.09	0.93
Hypomanic/manic symptom burden	0.813	1.904	0.43	0.67
Dependent Variable = Pulse Wave Velocity (N=31)				
Symptom Burden Model				
Depressive symptom burden	0.220	0.342	0.64	0.53
Hypomanic/manic symptom burden	0.211	0.398	0.53	0.60

Note: All models included age, gender, and tobacco exposure (pack*years)

chart review, exposure to first generation antipsychotics was significantly associated with change in systolic blood pressure, even after controlling for age, gender, and tobacco exposure.

The 25 individuals who received first generation antipsychotics were taking them for 23% of the observed follow-up period and were more likely to have bipolar I disorder (χ^2=5.25, df=1, p=0.02) though otherwise did not differ from the remainder of the sample. Controlling for diagnosis did not substantially alter the reported findings.

Table 12. Multivariate Linear Regression Models for Treatment Exposure on Arterial Stiffness Measures

	Beta	SE	t	*p*
Dependent Variable = Augmentation Pressure (N=35)				
Treatment Model				
Antidepressant exposure	-0.364	0.452	-0.80	0.43
Mood stabilizer/antipsychotic exposure	0.769	0.290	2.66	*0.013**
Individual mood stabilizer/antipsychotic classes (modeled separately)				
First generation antipsychotics	1.137	0.457	2.49	*0.019**
Second generation antipsychotics	0.522	0.684	0.76	0.45
Lithium	0.613	0.353	1.74	0.09
Valproic acid derivatives	0.267	0.597	0.45	0.66
Dependent Variable = Augmentation Index adjusted for heart rate of 75 (N=33)				
Treatment Model				
Antidepressant exposure	-0.675	0.606	-1.11	0.28
Mood stabilizer/antipsychotic exposure	0.221	0.362	0.61	0.55
Dependent Variable = Systolic Aortic Pressure (N=35)				
Treatment Model				
Antidepressant exposure	-0.846	1.016	-0.83	0.41
Mood stabilizer/antipsychotic exposure	1.539	0.650	2.37	*0.025**
Individual mood stabilizer/antipsychotic classes (modeled separately)				
First generation antipsychotics	3.275	0.930	3.52	*0.001**
Second generation antipsychotics	1.776	1.486	1.20	0.24
Lithium	0.745	0.803	0.93	0.36
Valproic acid derivatives	0.331	1.319	0.25	*0.80*
Dependent Variable = Pulse Wave Velocity (N=31)				
Treatment Model				
Antidepressant exposure	0.306	0.212	1.44	0.16
Mood stabilizer/antipsychotic exposure	0.129	0.147	0.88	0.39

Note: All models included age, gender, and tobacco exposure (pack*years)

* Significant at $p < 0.05$.

Reduced Models

Very similar results were obtained for significant findings in the primary and secondary analyses above in the sensitivity analysis using reduced models that included only age as a covariate. In the reduced model, manic symptom burden no longer crossed the threshold for statistical significance on FMD (p=0.06).

Exploratory Mediation Analyses

When manic symptom burden was modeled individually with physiological correlates, BMI produced the greatest reduction in the partial R^2 for manic symptom

burden on FMD (52%). The lack of an association between manic symptom burden and change in BMI in the subsample with available baseline data from chart review (N=28), however, failed to support potential mediation of manic symptoms on FMD by BMI. The addition of peripheral brachial systolic pressure to models reduced by 82% the partial R^2 between first generation antipsychotic exposure and central aortic augmentation pressure. In the sub-sample with chart review data at baseline (N=28), change in systolic blood pressure reduced the partial R^2 between first generation antipsychotic exposure and central aortic augmentation pressure as well (by 33%), rendering the initial association no longer significant. Models with peripheral brachial systolic blood pressure on aortic systolic blood pressure were not produced as the estimated aortic systolic blood pressure is partially derived from brachial systolic blood pressure. In the sub-sample, inclusion of change in systolic blood pressure reduced the partial R^2 for first generation antipsychotic exposure on aortic systolic blood pressure by 42% while first generation antipsychotic exposure remained significantly associated.

Discussion

Measures of manic symptom burden were proportional to vasculopathy. Patients with more manic/hypomanic symptoms had poorer endothelial function as determined by brachial artery FMD. FMD prospectively predicts vascular events in a manner that allows the clinical relevance of findings to be translated. In a study of brachial artery FMD from a community sample with a mean age of 67 years, an effect size of 2/3 standard deviations (SD) was associated with a 30% increased risk of cardiovascular events.[138] Another population-based study of 3,026 adults with a mean age of 61 (coincidentally identical to our sample) demonstrated a 25% increased risk of cardiovascular events corresponding to a 2/3 SD increase in FMD.[139] Our finding of 0.54 SD FMD from the manic symptom burden of 0.4% for a typical bipolar II to the manic symptom burden of 4% for a typical bipolar I[61] would be expected to translate to roughly a 20-25% increased risk of such events across this range of manic/hypomanic symptom

burden. As highlighted in Chapter III, survival analysis of cardiovascular mortality in bipolar disorder from the CDS similarly implicated manic symptom burden with cardiovascular mortality.[61] Although cross-sectional analysis suggested obesity as a possible mediator of this relationship, longitudinal data in our sub-sample with chart-review data failed to support a role for BMI as a mediator. First generation antipsychotic exposure was associated with arterial stiffness. In exploratory mediation models, this appears to be mainly due to elevation of peripheral systolic arterial pressure in the setting of first generation antipsychotics use. Long-term exposure to second generation antipsychotics and valproic acid derivatives were associated with cardiovascular risk factors, but not vasculopathy. The analyses could not reliably disentangle the effects of symptom burden independent of treatment exposure and vice versa. However, treatments were not associated with FMD, and manic symptom burden was not associated with arterial stiffness.

The demonstration of an association between first generation antipsychotics and arterial stiffness was not anticipated and has not been previously reported or studied. Improvement in vascular stiffness with antidepressant treatment in those with major depression, however, has been reported.[140] The alpha-1 adrenergic antagonism characteristic of many first generation antipsychotics would, if anything, be expected to reduce total peripheral resistance, and antipsychotics may induce orthostatic hypotension.[141] Unlike clinical trials, our analysis assessed medication exposure over several decades. Chronic administration of haloperidol has been shown to induce vasoconstriction in animal models.[142] D_2 receptors, which are antagonized by first generation antipsychotics, are also involved in the inhibition of sympathetic nerve activity.[143] D_2 antagonism could perhaps increase sympathetic tone and subsequently blood pressure. Hypertension is one of the most robust risk factors for arterial stiffness.[144] The relationship between antipsychotic exposure and arterial stiffness was not seen for pulse wave velocity, which assesses arterial stiffness across the aorta and

central conduit vessels,[145] which receive less adrenergic innervation than smaller, peripheral vessels[146] Thus, the pattern of results observed may lend support to the proposed mechanism regarding antipsychotic-induced sympathetic disinhibition.

There are several important limitations to this study. Participants were not randomized to treatment and results may be related to confounding variables. Our findings with first generation antipsychotics may be a result of a unique property of these medications or the fact that exposure to other medication classes, besides lithium and the broad category of antidepressants, was more limited in scope. Similarly, not all participants experienced manic symptoms. Depressive symptom burden did not appear related to vasculopathy although this relatively high acuity clinical sample may have underrepresented those with milder forms of depressive illness, restricting the range of exposure. The relatively small sample size limits power. With multiple comparisons, Type I error is also a concern. Defining primary outcomes *a priori* and pooling exposures attempted were employed to reduce this risk. Additionally, many of the variables treated continuously such as blood pressure and fasting lipids, may have been influenced by treatments such as antihypertensives or lipid-lowering medications. We elected to utilize continuous measures, rather than dichotomize data (e.g. analyze by triglycerides >= 150 mg/dL or on a lipid-lowering agent). Despite limited power, we were able to find several statistically significant associations. Our models included five variables for a total of 35 observations. This poses risk of overfitting, though eliminating variables for reduced models did not substantially alter the estimates. These data are also consistent with our previous report of a link between manic/hypomanic symptom burden and cardiovascular mortality.[61] The potential of this study to assess mediation was limited by sample size and cross-sectional assessment. Prospective collection of metabolic and vascular outcomes would have been required to establish mediation. We partially addressed this limitation through acquisition of baseline data on chart review in a sub-sample with available data. The design focused on physiological mediators

relevant to vascular function outcomes, assuming that behavioral factors mediated their effects through physiological measures. We identified potential mediation of the induction of arterial stiffness with antipsychotics by systolic blood pressure, which seems biologically plausible and amenable to further confirmatory study.

Existing data from the CDS allowed us to rigorously classify symptom burden and treatment exposures for assessment of impact on vascular function. These results add considerably to the developing literature on vasculopathy in mood disorders. Our cross-sectional vascular phenotyping methods were similarly rigorous and allowed us to identify associations between manic symptom burden and endothelial dysfunction and first generation antipsychotics with arterial stiffness. In exploratory analyses, we were further able to delve into potential mechanisms, such as elevated blood pressure on the relationship between first generation antipsychotics and arterial stiffness. Future studies may target other mediators within a causal change, such as variables that may link manic symptom burden with flow-mediated dilation and first generation antipsychotics with autonomic dysregulation. Due to their quantitative nature and sensitivity to all risk factors for vascular disease, vascular phenotyping methods may serve to further elucidate the mechanisms linking mood disorders to vascular disease.

CHAPTER V
HEALTH BEHAVIORS CONTRIBUTE TO ARTERIAL STIFFNESS LATER IN THE COURSE OF BIPOLAR DISORDER

Aims

Previous research has demonstrated impaired endothelial function in subjects with depression.[62,64,67] While one of these studies included some patients with bipolar disorder,[62] no other study has examined endothelial dysfunction and arterial stiffness exclusively in bipolar disorder. We sought to:

Study 1) Assess vascular function in a sample with bipolar disorder compared to controls

Study 2) Determine the relationship between course of illness and expected measures of arterial stiffness

We hypothesized that individuals with bipolar disorder would have poorer vascular function relative to matched controls. We further hypothesized that greater than expected arterial stiffness would be evident later in the course of illness.

Methods

Study 1 Sample

In total, 54 participants provided written informed consent for this study at the University of Iowa. Cases had a diagnosis of bipolar disorder (type I or II) or schizoaffective disorder, bipolar subtype based on chart diagnosis verified on clinical interview by the principal investigator. Controls were matched by gender and age (within 5 years). Controls were additionally selectively recruited to balance tobacco exposure with cases through targeted recruitment of smokers. We excluded participants if they were pregnant, currently abusing drugs or alcohol, taking phosphodiesterase inhibitors, or if they had a history of cancer, untreated thyroid disease, or Raynaud's disease.

Study 2 Sample

A total of 62 participants with a chart diagnosis of bipolar disorder (type I or type II) were recruited and consented for this IRB-approved study. Participants were included if they were between the ages of 20 and 46 and receive their clinical care from a staff physician at the University of Iowa Hospitals and Clinics. Participants were excluded if they had any history of cancer, untreated thyroid disease, or pregnancy.

Metabolic and Vascular Function Assessments

For Study 1, staff confirmed that participants fasted for at least 12 hours and had not smoked or drank caffeine for at least 2 hours prior. For Study 2, only 2 hours of fasting and cessation of smoking was required. Staff then measured vital signs, height, and weight. For Study 1, a blood sample was required. No blood was drawn for Study 2. In both studies, a member of the research team then obtained a health and psychiatric history.

For Study 1, a trained sonographer performed non-invasive vascular assessments of brachial artery endothelial function and arterial stiffness. Primary outcomes were flow-mediated dilation (FMD) and nitroglycerin (NTG)-mediated brachial artery vasodilatation, using previously described methods from Chapter IV.

For Study 1, secondary outcomes were pulse wave velocity, aortic systolic pressure, aortic augmentation pressure, and aortic augmentation index (adjusted for heart rate of 75 beats/minute), all assessed using SphygmoCor Technology as described in Chapter IV. Risk factors for vascular disease, such as BMI, fasting cholesterol and triglycerides, brachial arterial pressure, and insulin resistance (HOMA-IR) served as exploratory outcomes.

For Study 2, primary outcomes were augmentation index and pulse wave velocity. These outcomes were selected because of the subsequent availability of reference norms for these measures. Potential behavioral, instead of physiological, mediators served as a focus of Study 2. Physical activity was assessed with the long-version of the

International Physical Activity Questionnaire. Diet was assessed using a food frequency questionnaire, from which the Alternate Healthy Eating Index could be calculated. Medication histories were obtained through systematic review of pharmacy records over the past five years. The conceptual model for the focus on behavioral risk factors as proximal causes in Study 2 is illustrated in **Figure 8**. Age of onset and retrospectively estimated percent of time in depressive or manic episodes was determined from clinical interview.

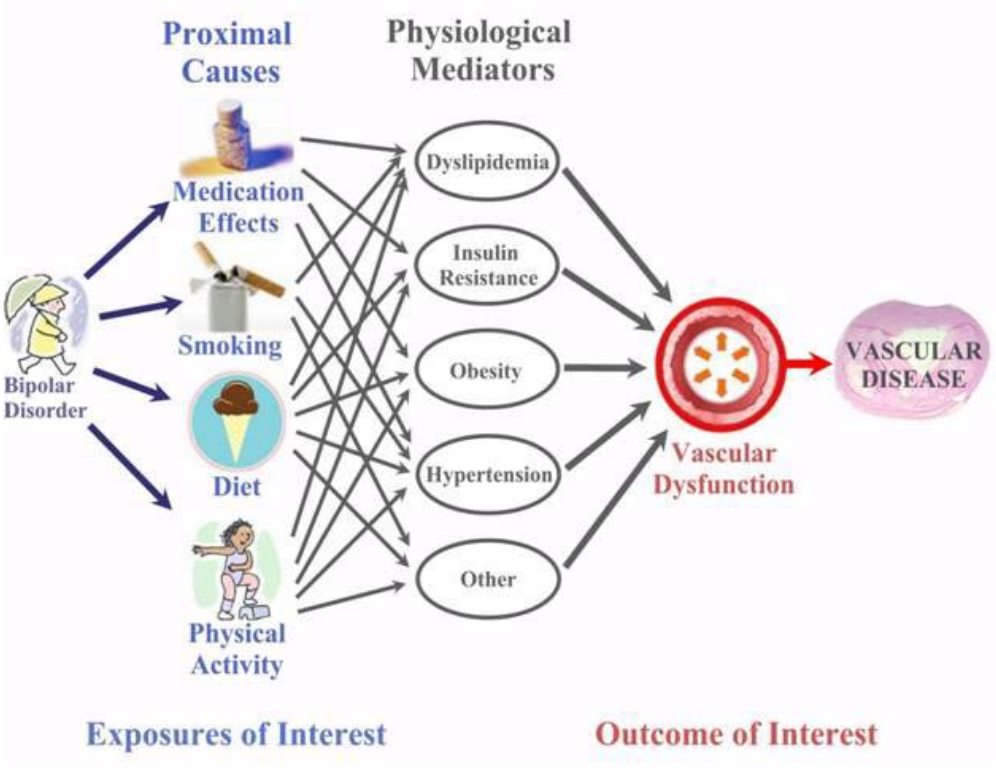

Figure 8. Conceptual Model Linking Aims of Study 2. Lifestyle and medication can lead to vascular dysfunction through various physiological mediators and cardiovascular risk factors. The project focused on identifying the most relevant proximal causes that may produce these changes and ultimately yield vascular dysfunction.

Statistical Analyses

For Study 1, sociodemographic and clinical variables were contrasted between groups using paired t-tests and McNemar's test for continuous and categorical data respectively. Primary, secondary, and exploratory outcomes were determined *a priori* as above and contrasted between groups using paired t-tests. All analyses were conducted using SAS 9.2.

For Study 2, expected values for our two primary outcomes, augmentation index and pulse wave velocity, were calculated from published norms using relevant clinical information for each participant.[147,148] Expected values for augmentation index were calculated from the following reference norms based on participant age, sex, height, and heart rate using the following formulas:[147]

Men: $148*Age^{0.267}*Height^{-0.576}*HeartRate^{-0.215}$

Women: $121*Age^{0.319}*Height^{-0.594}*HeartRate^{-0.196}$

Expected values for pulse wave velocity were calculated from the following reference norms based on participant age and blood pressure using the following formulas:[148]

Optimal Blood Pressure: $0.000*age + 0.00083*age^2 + 5.55$

Normal Blood Pressure: $0.000*age + 0.00099*age^2 + 5.69$

High Normal Blood Pressure: $0.000*age + 0.00105*age^2 + 5.91$

Grade I Hypertension: $0.000*age + 0.00118*age^2 + 6.17$

Grade II/III Hypertension: $0.044*age + 0.00085*age^2 + 5.73$

Expected values were compared to our observed values using paired t-tests. Impact of behavioral risk factors on arterial stiffness was evaluated in multivariate linear regression models.

Power was calculated to detect a clinically significant difference in flow-mediated dilation (FMD). In two population-based studies of brachial artery FMD, an effect size of 0.66 SD was associated with a 25-30% increased risk of cardiovascular events.[138,139] Our sample size was selected to detect an effect size of 0.66 SD with >90% power at an

alpha=0.05. For Study 2, this power calculation was applicable to the subgroup analyses on median split of age.

Results

Study 1 Sample Characteristics

Cases (N=27) did not differ from age- and gender-matched controls (N=27) across a variety of demographic and clinical characteristics as outlined in **Table 13**, although controls tended to be more educated (15.6 versus 14.3 years, *p*=0.06). There were no significant differences between cases and controls in BMI, systolic or diastolic blood pressure, race/ethnicity, tobacco exposure, history of hypertension, history of diabetes mellitus, or family history of heart disease. Cases had their first mood syndrome at a mean of 20.0 years of age.

Table 13. Demographic and Clinical Characteristics of Study 1 Sample (N = 54)

	Cases	**Controls**
	N=27	**N=27**
	Mean (SD)	
Age	32.1 (9.6)	32.4 (9.0)
Education (years)	14.3 (3.2)	15.6 (2.0)
Montgomery Asberg Depression Rating Scale[149]	16.8 (12.4)	1.7 (3.4)
Young Mania Rating Scale[150]	7.7 (7.6)	0.7 (1.2)
Pack years (smoking)	6.6 (13.9)	6.7 (10.6)
Body mass index (kg/m^2)	28.2 (6.4)	26.7 (5.0)
Systolic blood pressure (mmHg)	117 (12)	115 (14)
Diastolic blood pressure (mmHg)	69 (11)	71 (9)
	N (%)	
Female gender	11 (41%)	11 (41%)
White, not Hispanic	18 (67%)	20 (74%)
Ever smoked tobacco	16 (59%)	17 (63%)
Hypertension	1 (4%)	1 (4%)
Diabetes mellitus	1 (4%)	1 (4%)
Family history of heart disease	8 (30%)	9 (35%)

Data for primary outcomes was complete. Pulse wave velocity could not be obtained for technical reasons on two cases and one control and pulse wave analysis could not be reliably obtained on one case. Data on LDL-cholesterol was missing for one control. Due to a laboratory error, fasting insulin was missing from three participants.

Table 14. Demographic and Clinical Characteristics of Study 2 Sample (N = 62)

	Mean (SD)
Age	33 (7)
Education (Years)	15.3 (2.0)
Pack years (smoking)	8 (11)
Body mass index (kg/m^2)	30.3 (6.9)
Systolic blood pressure (mmHg)	117 (9)
Diastolic blood pressure (mmHg)	68 (9)
Physical activity (met*mins/week)	5330 (4933)
Alternate Healthy Eating Index score	36.8 (10.2)
	N (%)
White, not Hispanic	18 (67%)
Female gender	40 (64%)
Employed	35 (56%)
Education	
High school graduate or less	6 (10%)
At least some college	56 (90%)
Bipolar I diagnosis	36 (58%)
Hypertension	4 (6%)
Diabetes mellitus	2 (3%)
Ever smoked tobacco	37 (60%)

Study 2 Sample Characteristics

Sociodemographic and clinical characteristics of the Study 2 sample is detailed in **Table 14**. Individuals in sample 2 had a mean (SD) age of 33 years and ranged from 20-46 years. A slight majority of the sample was female. Almost ⅔ of the sample (64%) was female. The mean body mass index was in the obese range (30.3 kg/m^2).

Participants retrospectively estimated spending a median of 22% (mean 28%) of time depressed and 7% (mean 12%) of the time manic in the past decade or since onset of illness if within the past decade. These retrospective estimates were considered of questionable validity, particularly the retrospective estimate of manic symptom burden which is much higher than would be expected from Collaborative Depression Study (CDS) data based on the proportion of the sample with bipolar I (observed mean of 12.2% versus expected mean of 6.8%).

Main findings

Vascular and metabolic assessments did not distinguish cases from controls from Study 1 as reported in **Table 15**. No significant difference was found between the two groups for primary outcomes (flow-mediated dilation (t=0.76, df=26, *p*=0.45) and nitroglycerin-mediated dilation (t=1.61, df=26, *p*=0.12)) or secondary outcomes (aortic augmentation pressure (t=-0.57, df=25, *p*=0.58), adjusted augmentation index (t=0.93, df=25 *p*=0.36), pulse wave velocity (t=-0.66, df=23 *p*=0.52), and systolic aortic pressure (t=-0.44, df=25, *p*=0.66)). Cases had significantly greater insulin resistance than controls (t=2.23, df=23, *p*=0.036). On subgroup analysis, this difference in HOMA-IR (cases minus controls) was significant and quantitatively higher only for those on antipsychotics (1.60) or those not on lithium (1.67). Lithium use was inversely associated with antipsychotic use (Fisher's exact *p*=0.004). Therefore these groups were highly overlapping. Those on antipsychotics or on lithium did not appear to differ otherwise from the remainder of the sample except those on lithium had a significantly lower score on the Young Mania Rating Scale (mean of 1.4 versus 9.2, t=4.2, df=25, p=0.0003). The groups did not differ on other exploratory outcomes.

In Study 2, measures on the Alternate Healthy Eating Index were much worse than expected from the U.S. General Population. Based on thresholds for the Healthy Index Rating (score 0-100) from the United States Department of Agriculture (www.cnpp.usda.gov/HealthyEatingIndex.htm), an estimated 11-12% of the population

Table 15. Vascular and Laboratory Outcomes for Study 1

	Cases	Controls
	Mean (SD)	**Mean (SD)**
Vascular testing:		
FMD (%)	8.4 (3.6)	7.6 (4.8)
NTG-mediated dilation (%)	15.2 (8.8)	12.5 (4.8)
PWV (m/s)	7.2 (1.1)	7.2 (1.2)
AIX at 75 bpm	6.9 (18.0)	4.6 (15.3)
Augmentation pressure (mm Hg)	3.4 (5.1)	4.0 (5.6)
Aortic systolic pressure (mm Hg)	103 (11)	104 (12)
Laboratory values:		
Fasting glucose (mg/dL)	92 (12)	90 (7)
HOMA-IR†	2.4 (1.7)	1.3 (0.8)
HDL-cholesterol (mg/dL)	46 (13)	49 (13)
LDL-cholesterol (mg/dL)	97 (23)	92 (30)
Triglycerides (mg/dL)	121 (55)	118 (90)

† $p<0.05$.

has a good diet (>80), 73-76% of the population needs improvement (51-80), and 14-15% of the population has a poor diet (<51). Extrapolating these thresholds to the range of the Alternate Healthy Eating Index (2.5-87.5), 0% of our sample had a good diet, 65% had a diet in need of improvement, and 35% would be classified as having a poor diet.

Compared to reference norms, participants in Study 2 had a greater than expected augmentation index (10.5 vs. 7.7, t=2.1, df=61, *p*=0.04) but not pulse wave velocity (6.9 vs. 6.7 m/s, t=1.5, df=61, *p*=0.14). When stratified by median age, those older than the median age had greater stiffness of elastic arteries (augmentation index) and the aorta (pulse wave velocity) than expected based on normative data, while the younger half of the sample was in line with published, age-based norms as highlighted in **Figure 9** and **Figure 10**. Thus, the greater than expected for age values for arterial stiffness measures were seen only in the older portion of our sample.

The mean (SD) estimated age of onset was 19.3 (6.2) years. Age was highly correlated with retrospectively estimated illness duration (r=0.72, *p*=0.001). When the sample was divided by median chronicity (duration of illness * retrospectively estimated percent time depressed or manic), the sample with greater estimated affective symptom burden had a significantly greater than expected augmentation index (t=5.7, df=29, *p*=0.0007) and approached significance for pulse wave velocity (t=1.9, df=29, *p*=0.07). The association with augmentation index remained significant when stratifying by retrospectively estimated depressive symptom burden (t=2.5, df=29, *p*=0.02) and manic symptom burden (t=2.5, df=29, *p*=0.03). The half of the sample with greater depressive but not manic symptom burden, had significantly greater than expected pulse wave velocity (t=2.1, df=29, *p*=0.04).

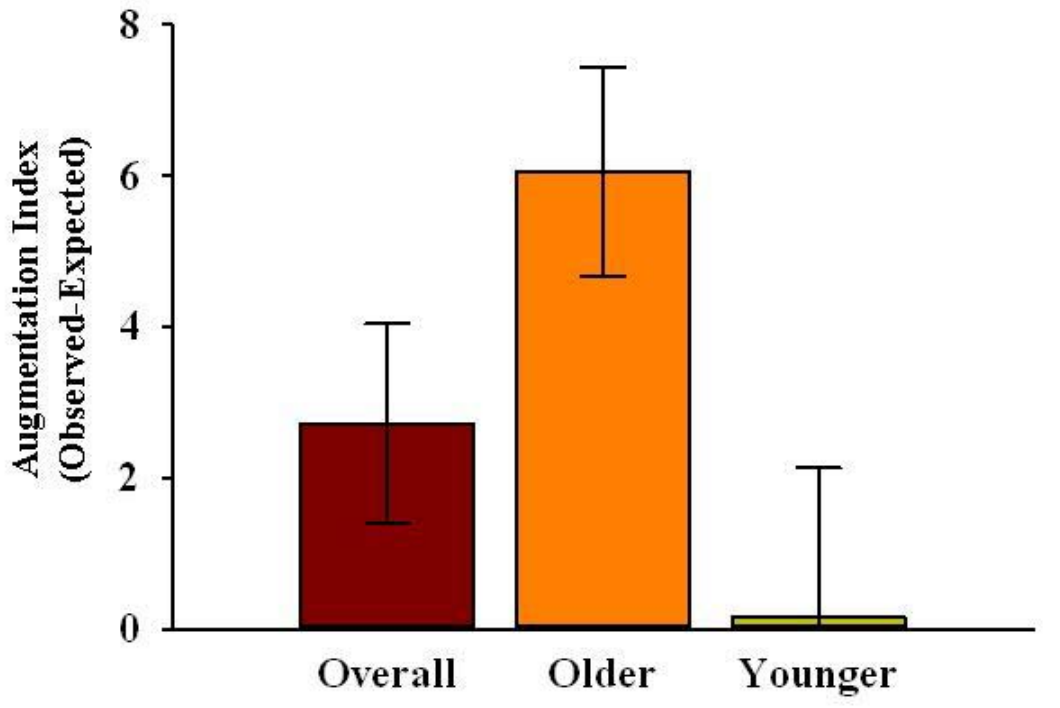

Figure 9. Augmentation Index Relative to Reference Values. The augmentation for participants was greater than expected from age, height, and heart rate based norms. Greater arterial stiffness than expected was seen for the older but not younger half of the sample on median split.

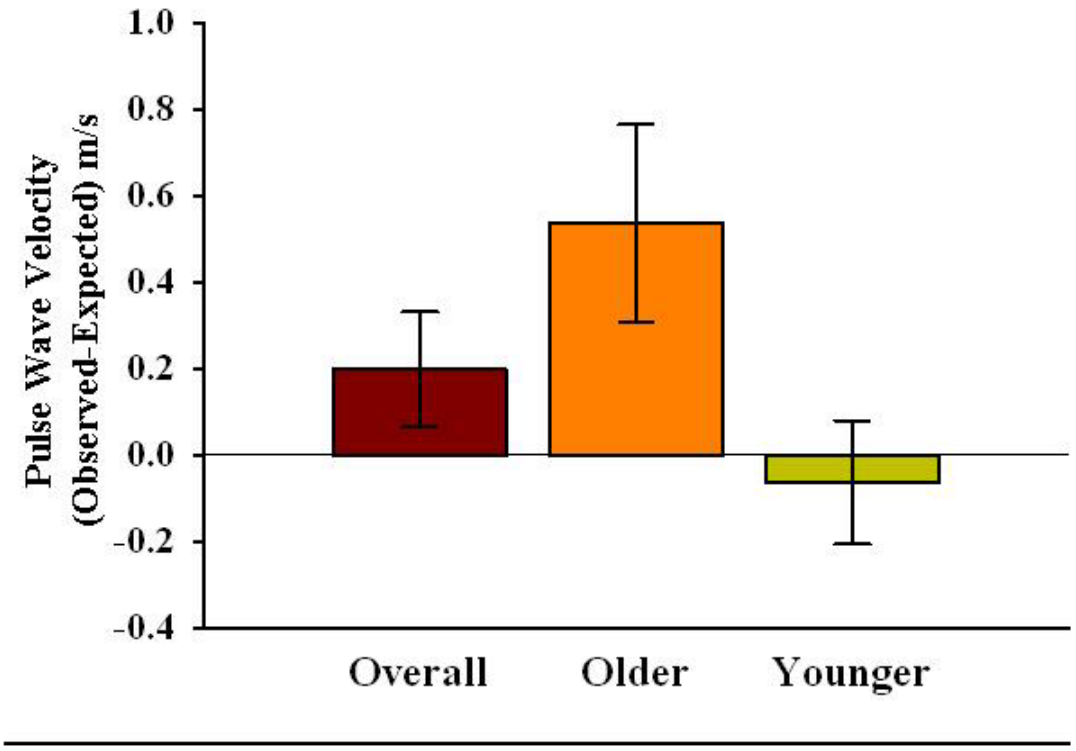

Figure 10. Pulse Wave Velocity Relative to Reference Values. The pulse wave velocity for participants in the older but not younger half of the sample was greater than expected from age and blood pressure based norms.

In multivariate models for the full Study 2 sample including age, gender, body mass index, and behavioral risk factors (diet, physical activity, tobacco exposure), revealed a significant effect of only age on both arterial stiffness measures and body mass index on pulse wave velocity as shown in **Table 16**. When reduced models (including age, gender, and individual risk factors to avoid over-fitting) were applied to the older half of the sample, greater physical activity was significantly associated with a lower augmentation index (partial R^2=0.18, p=0.04), and better diet (Alternate Healthy Eating Index Score) approached significance with slower pulse wave velocity (partial R^2=0.15, p=0.054). The effects of physical activity and diet appeared independent of body mass index, which was also significantly associated with both arterial stiffness measures. The

inclusion of exposure to antipsychotics or mood stabilizers did not substantially alter these findings.

Table 16. Multivariate Linear Regression Models for Relationship between Behavioral Risk Factors and Arterial Stiffness

	Beta	SE	t	*p*
Dependent Variable = Augmentation Index				
Alternate Healthy Eating Index	-0.085	0.119	-0.72	0.47
Physical activity (met*mins/week)	-0.0002	0.0003	-0.97	0.33
Body Mass Index	0.318	0.181	1.76	0.08
Dependent Variable = Pulse Wave Velocity				
Alternate Healthy Eating Index	0.004	0.013	0.28	0.78
Physical activity (met*mins/week)	0.000	0.000	0.34	0.74
Body Mass Index	0.064	0.019	3.29	*0.001*

Note: All models controlled for age, gender, and tobacco exposure (pack*years)

Discussion

Although the previous literature has consistently and convincingly demonstrated an increased risk for cardiovascular morbidity and mortality in people with bipolar disorder, we found no evidence of vasculopathy in our young sample from Study 1, which was balanced for tobacco exposure. In exploratory analysis of risk factors for vascular disease, cases with bipolar disorder demonstrated greater insulin resistance than matched controls, consistent with the results of other studies noting a relationship between bipolar disorder and insulin resistance or type 2 diabetes.[44]

Relatively young individuals might not show evidence of vasculopathy early in their disease course. With a mean age of 32 years, our Study 1 sample was much younger than those of prior studies demonstrating an association between mood disorders and impaired vascular function (average age of 43-72 years).[62,64,67] These studies are summarized in **Table 17**. If the increased cardiovascular risk develops long-term over the course of illness, Study 1 may have been less able to identify whose vasculopathy had

progressed sufficiently to manifest itself. Our Study 2 findings support this hypothesis. Greater than expected arterial stiffness was seen only in the older half of the sample, and this appeared to reflect retrospectively estimated symptom burden. In this study, symptom burden could not be as rigorously assessed prospectively (See Chapters III and IV) though nonetheless appeared relevant.

Table 17. Studies on Vascular Function in Mood Disorders

Study	Sample	Measure	Effect Size
Rybakowski et al. 2006[62]	31 unipolar or bipolar (mean 43 years) vs. 18 healthy controls	Change in augmentation index with albuterol	Insufficient data to estimate
Lavoie et al. 2010[64]	23 with MDD, 23 with MinD, 277 controls (mean 59 y/o)	Nuclear medicine variation of FMD	0.63 (MDD) 0.52 (MinD)
Paranthaman et al. 2010[67]	25 with depression vs. 21 non-depressed (mean 72 y/o)	Acetylcholine Response of gluteal fat arteries (biopsy) to acetylcholine	> 3? † ~0.75 (PWV)

Note: MDD=Major Depressive Disorder, MinD=Minor Depressive Disorder, PWV=Pulse Wave Velocity

† Suspect standard error inappropriately recorded as standard deviation in manuscript.

In Study 1, the case and control groups were also balanced with respect to tobacco exposure. Because smoking is important risk factor for cardiovascular disease and highly prevalent among those with bipolar disorder,[28] balancing groups by smoking would limit detection of any differences attributable to this mediator. Despite similar BMI, cases with bipolar disorder had greater insulin resistance, suggesting this may be a relevant risk factor identifiable even early in the course of bipolar illness. Insulin resistance appeared to be related to antipsychotic exposure, as previously reported,[151] and known biological effects of these agents.[152] Conversely, those on lithium had less apparent insulin

resistance, perhaps because lithium exerts insulin-like effects[153] or because those not taking lithium were more likely to be on antipsychotics.

There are several limitations to these studies. Both studies involved a cross-sectional assessment. Therefore, temporality cannot be ascertained. It is possible that the older half of the sample in Study 2 had greater arterial stiffness from an early age. Thus, we must temper any conclusions related to the development of vasculopathy over course of illness in this cross-sectional study. However, when considered in the light of prior data (Chapter III and IV) showing prospectively assessed manic symptom burden to be related to subsequent cardiovascular mortality and endothelial function, there is converging evidence that vascular risk is acquired over the long-term course of illness. In both studies, bipolar disorder was broadly defined, although an even broader sample that included unipolar major depression identified impairment in vascular function in older subjects.[62] Although groups were balanced for tobacco exposure, other behavioral risk factors may not have been as well balanced between groups. Targeted recruitment of smokers may have over-represented other maladaptive health behaviors among controls in Study 1. Study 2 focused on single measures of physical activity and diet. The Alternate Healthy Eating Index, while having the advantage of being a summary measure for use in linear regression, may not optimally capture vascular risk secondary to diet. Exploratory analysis of other dietary measures, such as saturated fat or trans fat, may provide added value to the determining the impact of diet on risk for vascular disease.

Greater than expected vasculopathy was seen later in the course of bipolar disorder. Insulin resistance may represent an early risk factor, perhaps secondary to antipsychotic exposure. However, the arterial stiffness seen later in the course of bipolar disorder appears related to maladaptive health behaviors, such as poor diet and physical activity, which may be amenable to intervention early in the course of illness, prior to the onset of vasculopathy. Integration of health promotion interventions addressing these

behavioral risk factors presents a potential opportunity for clinicians working with this at-risk population to impact risk.

CHAPTER VI

CONCLUSIONS

Summary of Critical Findings

Chapter I detailed a convergence of large scale epidemiological findings reporting a strong association between bipolar disorder and mortality secondary to vascular disease. In the largest study to date, the standardized mortality ratio for cardiovascular mortality in bipolar disorder was 1.94 in men and 2.65 in women.[23] A greater prevalence of risk factors for vascular disease has been consistently reported and may explain this mortality association. However, a variety of potential causes for the elevated risk of vascular disease in bipolar disorder have been proposed, ranging from issues related to access, health behaviors, the impact of treatment, and factors intrinsic to the illness itself. The high magnitude of the association renders Berkson's bias unlikely to fully explain the association; however, all mortality samples have involved inpatient samples. The impact of any such selection bias is difficult to estimate though the large magnitude and consistent replication of the association render the findings unlikely to be fully explained by selection bias.

Chapter II discerned the relationship between bipolar and related affective disorders and vascular disease in a cross-sectional study of a nationally representative sample from the contiguous United States. This study did not use a clinical sample and did not rely upon a prior diagnosis of a mood disorder. Rather, all participants were screened with a structured diagnostic instrument. In this sample, mood disorders were associated with self-reported vascular disease with a significant odds ratio of 1.87 in men and 1.72 in women. The highest magnitude association was seen with women with bipolar disorder (OR=4.14) although the precision of the estimates in those with bipolar disorder was limited by the small number of observed cases with vascular disease in the 2.1% of the full NCS-R sample identified as having bipolar disorder.[154] Of interest, the

findings appeared independent of available risk factors for vascular disease. This suggests that not all of the effects of mood disorders are mediated through established risk factors for vascular disease, although the potential for residual confounding persists.

Chapter III established a dose-response between manic symptom burden and cardiovascular mortality in the CDS, a large, well-characterized prospective cohort study of individuals with mood disorders. The magnitude of this association was such that for spending 10% more of follow-up with clinically significant manic or hypomanic symptoms was associated with a 27% increased risk in mortality. In Chapter IV, this finding was replicated with mechanistic insight. In this small sample of individuals who had completed the CDS, manic symptom burden was associated with endothelial dysfunction, as evidenced by reduced flow-mediated but not nitroglycerin-mediated vasodilation. Additionally, exposure to first generation antipsychotics was associated with greater arterial stiffness. This latter finding appeared to be mediated by changes in blood pressure. This finding has not been reported before and warrants replication and study of potential mediators such as antipsychotic-induced autonomic dysfunction. The unexpected lack of an association with depressive symptom burden could be due to a restriction of range in this relatively high acuity sample of individuals with mood disorders, of whom ¾ were recruited as inpatients.

The case-control study (Study 1) from Chapter V failed to demonstrate greater impairments in vascular function in a young sample with bipolar disorder relative to matched controls. In light of the existing data reported herein suggesting a role for symptom burden on vascular risk, this may be due to the young age of the sample, which included individuals early in their course of illness. This may also have been due to a balancing of behavioral risk factors between groups though targeted recruitment of controls who smoke tobacco. In a follow-up to this study, we utilized age-based norms of arterial stiffness measures to determine if age / duration of illness indeed appeared to be relevant as hypothesized. With consistency across arterial stiffness measures, we

found the older half of the sample, but not the younger half of the sample, had significantly greater than expected arterial stiffness when compared to age-based reference values. Crude measures of retrospectively estimated symptom burden appeared to support the role of course of illness in explaining this finding for both depressive and manic symptoms. Multivariate models suggested that health behaviors related to diet and physical activity play a role in the development of such stiffness though this effect, as well, was only evident in the older half of the sample. The adverse effects of these behaviors may not have been evident in the younger portion of the sample whose arterial stiffness indices did not deviate from expected values.

Limitations

The studies presented herein involved exclusively observational designs. Unfortunately, the key exposures of interest, related to symptom burden and course of illness, are not amenable to experimental study. Participants cannot be "randomized" to different levels of symptom burden. Even the long-term effects of medication exposure, a variable of interest, may be difficult to study using an experimental study design. It may not be ethical to randomize individuals to treatments for the sole purpose of assessing adverse effects. Further, animal models do not consistently replicate the effects of these medications in human populations, such as weight gain.[155] Additionally, it may not be feasible to include participants in clinical trials of adequate duration to observe vascular endpoints. Longer-term trials of antipsychotics have had high rates of dropouts and change in medications due to inadequate response or tolerability. In a large National Institutes of Health funded trial of the relative effectiveness of antipsychotics, only 26% of participants remained on study medicine at the end of Phase 1 (18 months).[156] This reality severely impedes the ability of experimental designs to address questions related to long-term adverse effects, apart from very high risk samples that may not generalize to the broader population of individuals in treatment for bipolar disorder.

Another limitation of the studies reported herein relates to the use of either a cross-sectional assessment alone or a cross-sectional assessment following prospective study of the exposures of interest. To definitively establish temporality and to appropriately study mediation, vascular and metabolic assessments should be performed before and after prospective assessment of the exposures of interest.

Issues related to confounding and mediation pose a vexing problem for the study of vascular risk in mood disorders. There exist a variety of potential confounding variables, many of which defy reliable measurement. Health behaviors, for instance, such as diet and physical activity, are notoriously difficult to reliably measure. Depending on one's perspective and how the causal chain is conceptualized, a variable may represent a confounder or a mediator. For instance, it is possible that individuals with major depression tend to be less active, regardless of mood, and this inactivity predisposes to vascular risk. In this case, it would be important to control for physical activity as a confounder. Alternatively, depressed mood could result in physical inactivity, which increases risk of vascular disease. In this case, physical activity is arguably best classified as a mediator, or an intermediate on the causal chain between depression and vascular disease. The reported analyses have tended to broadly consider behavioral and physiological variables as potential mediators. However, these variables were nonetheless included in initial or subsequent models as covariates, allowing exploration of potential mediation (with acknowledgement of limitations therein) or alternatively addressing confounding.

Future Directions

Experimental or well-designed observational studies of the association between antipsychotic exposure and arterial stiffness from Chapter IV could confirm these findings and provide an opportunity to study mediators. Although of great interest, studying the impact of affective symptom burden over the long-term course of illness is a monumental challenge. A prospective cohort study of individuals with mood disorders

that rigorously assessed vascular phenotype and potential behavioral, psychological, and physiological mediators throughout would be ideal. Cost may threaten the feasibility of such a design although creative means of embedding vascular phenotyping methods and metabolic assessments in a broader purpose study, from its inception, is possible. Any such opportunities would be worth pursuing. The excess burden of vascular disease presents a major public health problem for this at risk population.

Final Conclusions and Implications

Individuals with bipolar disorder face a frighteningly large burden of excess death from vascular disease. This finding is not limited to clinical samples, but may be seen in representative community samples. The burden of clinically significant manic symptoms demonstrates a dose-dependent relationship with cardiovascular mortality, an effect that may be secondary to the development of endothelial dysfunction. First generation antipsychotic use, poor diet, and limited physical activity may also contribute to arterial stiffness. An excess risk of vasculopathy does not appear present early in the course of illness, but appears to be acquired over the long-term course of illness in mood disorders.

Clinicians working with individuals with bipolar disorder should be mindful of this elevated vascular risk and manage accordingly. There exists considerable opportunity to address vascular risk early in the course of illness, prior to the onset of the greater than expected vasculopathy.

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