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History of Manic and Hypomanic Episodes and Risk of Incident Cardiovascular Disease: 11.5 year Follow-up from the Baltimore Epidemiologic Catchment Area Study

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Abstract

Background—While several studies have suggested that bipolar disorder may elevate risk of cardiovascular disease, few studies have examined the relationship between mania or hypomania and cardiovascular disease. The purpose of this study is to examine history of manic and hypomanic episodes as an independent risk factor for cardiovascular disease (CVD) during an 11.5 year follow-up of the Baltimore Epidemiologic Catchment Area Follow-up Study.

Methods—All participants were psychiatrically assessed face-to-face based on Diagnostic Interview Schedule in 1981 and 1982 and were categorized as having either history of manic or hypomanic episode (MHE; n = 58), major depressive episode only (MDE; n=71) or no mood episode (NME; n=1339). Incident cardiovascular disease (CVD; n = 67) was determined by self-report of either myocardial infarction (MI) or congestive heart failure (CHF) in 1993–6.

Results—Compared with NME subjects, the odds ratio for incident CVD among MHE subjects was 2.97 (95% confidence interval: 1.40, 6.34) after adjusting for putative risk factors.

Conclusions—These data suggest that a history of MHE increase the risk of incident CVD among community residents. Recognition of manic symptoms and addressing related CVD risk factors could have long term preventative implications in the development of cardiovascular disease in the community.

Keywords

Mania; Hypomania; Cardiovascular Disease; Bipolar Disorder; ECA

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All authors declare that they have no conflicts of interest.

Background

Estimated to affect as much as 6% of the general population (Akiskal, 2007; Judd and Akiskal, 2003), bipolar disorder (BPD) (Angst and Cassano, 2005; Angst, et al, 2005) has been associated with high prevalence of cardiovascular disease (CVD) (up to 49%) (Beyer, et al, 2005; Fenn, et al, 2005; McIntyre, et al, 2006; Thompson, et al, 2006). However, the results of past comparative studies examining the risk of CVD between patients with BPD and without have been mixed. Cross-sectionally, studies based on clinical samples have reported that BPD patients have high prevalence of CVD risk factors such as metabolic syndrome, obesity, hypertension, high cholesterol, diabetes, and smoking (Kilbourne, et al, 2004; Newcomer, 2004; Taylor and MacQueen, 2006). Yet, based on a survey of 4181 residents in Germany, Baune et al. reported no significant increase in the risk of coronary heart disease among participants with BPD in the community (Baune, et al, 2006).

Unlike cross-sectional studies, few available longitudinal studies attempted to address the direction of causality issue in the relationship between BPD and CVD. Two studies have indicated that the cardiovascular standardized mortality ratio (SMI) is higher for those with BPD in comparison to those with major depressive disorder (MDD) and to the general population (Angst and Cassano, 2005; Angst, et al, 2005; Osby, et al, 2001). In contrast, Lin et al (2008) recently reported no higher risk of myocardial infarction among BPD patients during a 6-year follow up after an acute hospitalization for a mood episode based on the Taiwan National Health Insurance Research Database (Lin, et al, 2008). However, these studies have either addressed cardiac mortality only (Angst, et al, 2005; Osby, et al, 2001) or relied on case registry with uncertain validity of psychiatric diagnosis (Lin, et al, 2008; Osby, et al, 2001).

Furthermore, few previous studies have specifically examined the relationship between manic episodes and CVD. Numerous studies have established that depressive symptoms or episodes increases risk of incident cardiovascular disease in the community (Rugulies, 2002) and cardiac morbidity and mortality in patients with established heart disease (Barth, et al, 2004; van Melle, et al, 2004; Wulsin and Singal, 2003). Manic or hypomanic episodes are as common and prominent features of BPD as depressive episodes are. It is not known, however, whether or not the relationship between BPD and CVD could be attributed to depressive phase of BPD only as no previous study has examined mania or hypomania as an independent risk factor for CVD.

The purpose of this study was to examine manic or hypomanic episodes as a risk factor for incident CVD during the 11.5 year follow-up of community residents in the Baltimore Epidemiologic Catchment Area (ECA) follow-up study. Previously, Pratt et al, based on the same cohort, reported a strong association between syndromal depression and incident myocardial infarction (Pratt, et al, 1996). Taking into account recent observations of the putative association between bipolar disorder and CVD, this study aims to expand upon the findings reported by Pratt, et al by examining the role of mania and hypomania. In this study, we examined manic and hypomanic episodes (MHE) as an independent risk factor for CVD while adjusting for putative risk factors, including DSM III major depressive episodes (MDE). As a secondary aim, we also examined whether manic dimensional symptom scores were associated with incident CVD.

Methods

Sample

The Baltimore ECA Follow-up Study is a longitudinal study of mental disorders and physical illness among community residents in East Baltimore (Anthony, et al, 1995; Eaton,

et al, 1997; Regier, et al, 1984). Further details of the Baltimore ECA follow-up study and methods can be found elsewhere (Badawi, et al, 1999; Eaton, 1985; Eaton, et al, 2007). Of 3481 original participants who completed the interview during Wave I (1980), 2768 were re-interviewed a year later during Wave II (1981). During Wave III (1993–1996), 75 % of the surviving cohort (n=1920) were re-interviewed, and the final sample (n=1468) for this analysis includes participants from Baltimore ECA follow-up Wave I-III with adequate data to diagnose manic or hypomanic episode by Wave II and to determine the presence or absence of incident cardiovascular disease (CVD) at wave III. In order to assess for new incidence of CVD, those who reported “heart trouble” at Wave I or II (n = 182) were excluded from the analysis. Also excluded were those with incomplete DIS data at Wave I or II (n = 184), and response of “I don’t know” or incomplete data on CVD questions on Wave III (n = 86).

Psychiatric Assessment: Diagnostic Interview Schedule (DIS) (Robins, et al, 1981)

The DIS is a structured interview designed to be administered by a trained layman interviewer and consists mostly of yes or no questions design to diagnose mental disorders based on the DSM-III criteria. The DIS has been shown to have good reliability and acceptable validity (Robins, et al, 1981)(Bass, et al, 1988). All subjects in the analysis were classified into three affective categories based on DIS conducted during Wave I and II as following:

1. **Manic and Hypomanic Episode (MHE) Group (n = 58):** Subjects in this category met the criteria for at least one manic or hypomanic episode during their lifetime by Wave II. Included in this categories are those (n =21) who met diagnostic criteria for both MHE and MDE.

Manic episode (n=13): Subjects met the criteria for DSM-III Manic episode which included reporting feeling euphoric for a week or more in addition to three other manic symptoms, or reported irritable mood for a week or more in addition to at least four other manic symptoms.

Hypomanic episode (n=45): Subjects reported feeling euphoric for a week or more, but had less than three other manic symptoms and did not meet the criteria for a DSM-III manic episode or, participants reported an irritable mood for a week or more in addition to three other manic symptoms. .

2. **Major Depressive Episode (MDE) only group (N=71):** Subjects met the lifetime diagnostic criteria for DSM-III MDE by Wave II based on DIS version III, which included reporting dysphoric mood and four other depressive symptoms lasting two or more weeks, but did not meet the criteria for history of manic or hypomanic episode.
3. **No Mood Episode group (NME) (N= 1339):** Subjects had no history of manic or hypomanic episodes or major depressive episodes by Wave II.

Manic Symptom Count: A 0–8 score was attributed to each subject based on the total number of DSM IV manic symptoms reported during lifetime. Unlike the symptom counts for affective category classification, symptoms for total manic symptom count did not have to be experienced concurrently during a mood episode.

Primary outcome: Incident CVD at Wave III

Detailed questions about health status were inquired during the Wave III (1993–1996). The ECA survey posed the question “Have you ever had heart trouble?” The participants who endorsed “heart trouble” were then asked about five specific conditions: rheumatic fever, rheumatic heart disease, angina pectoris, MI and CHF. Self Report of “incident CVD” was

defined as new onset MI or CHF related to “heart trouble.” Due to the variable sensitivity and specificity of detecting true CHD by self-report of angina pectoris (Bass, et al, 1988), we did not use self-report of angina pectoris as an outcome variable.

Other covariates

In all three waves of the Baltimore ECA study, information was collected about participants' sociodemographic characteristics; history of common general medical illnesses (i.e. hypertension and diabetes mellitus, and stroke), abuse and dependence of alcohol, smoking, use of psychotropic medications, and perception of overall health.

Statistical Analysis

A series of comparisons of sociodemographic, general medical, and mental health variables among three groups (MHE, MDE, and NME) were conducted using Fisher's exact tests for categorical variables. For continuous variables, independent samples t-tests were used to compare means of the MHE group separately to the MDE group and the NME group. Correlations between sociodemographic, health, and mental health variables and CVD were examined using univariate logistic regression models.

To assess the risk of CVD in mania and hypomania after controlling for other risk factors, logistic regression analysis was performed to obtain adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Diagnosis of MHE, MDE and manic symptom count were the main predictor variables, and incident CVD was the outcome of interest. Demographic variables that were significant predictors of CVD in the univariate analysis were adjusted for in the multivariate model. Medical, behavioral, and psychotropic medication variables were subsequently added to the model. Variables were retained in the model if they were significant at the level of $P < .10$ or if their removal altered the ORs associated with MHE or manic symptom count by $>20\%$. In models where MHE was the main predictor variable, a linear combination estimator test was run to compare the odds of MHE to MDE to examine significant differences between MHEs and MDEs.

Results

Subjects in the MHE, MDE, and NME groups differed on several sociodemographic characteristics at baseline (Table 1). MHEs were younger (mean: 43.1, SD= 7.8) than MDEs (mean= 48.1, SD= 10.3) and NMEs (mean= 52.1, SD= 15.7). MHEs (41.4 %) were less likely to be Caucasian than MDEs (66.2 %) and NMEs (62.9 %). MHEs (37.9 %) and MDEs (38.0 %) were both less likely to be married than NMEs (52.7 %). There were no significant differences among the groups in mean years of education or gender. Rates of attrition during follow-up also did not differ significantly between groups; 51.7% of NMEs, 56.8 % of MDEs, and 57.4 % of MHEs from the original Wave I cohort continued to participate through Wave III of the study. MHEs differed from MDEs and NMEs on several known behavioral and medical risk factors for CVD (Table 1). History of alcohol abuse or dependence was most prevalent among MHEs (39.6 %), followed by MDEs (20.6 %), and NMEs (14.7 %). Likelihood of smoking one or more packs of cigarettes per day followed the same trend with MHEs reported prevalence at 58.5 %, MDEs at 47.1 %, and NMEs at 40.7 %. MHEs (15.2 %) and MDEs (14.9 %) reported their health to be fair or poor more often than NMEs (7.35 %). There were no significant differences between groups in their history of diabetes, hypertension, or stroke. With respect to psychotropic medications, more MHEs reported being on lithium (7.0 %) and antipsychotics (20.7 %) than MDEs (lithium (1.4 %) and typical antipsychotics (16.9 %)) and NMEs (lithium (0.37 %) and typical antipsychotics (3.14 %)). Both MHEs (26.0 %) and MDEs (23.2%) were more likely to have reported taking antidepressant medications than NMEs (4.81 %).

At 11.5 year follow-up, incidence of CVD was highest among MHEs, with 5 (8.77 %) of the 58 participants reporting incident CVD. Prevalence of CVD among MDEs was 7.14 % with 5 of the 71 participants reporting incident CVD. NMEs accounted for 57 (4.27 %) participants with incident CVD (Table 2).

Table 3 shows the unadjusted odds for sociodemographic and health and mental health related variables as risk factors for incident CVD. Among demographic variables, older age, male gender, and fewer years of education were associated with incident CVD. Among health variables, history of hypertension, smoking, and abuse or dependence of drugs or alcohol was associated with incident CVD. Self report of good or excellent health was negatively associated with incident CVD. With respect to mental health variables, history of manic episodes and manic symptom count was associated with incident CVD, as was use of lithium, typical antipsychotics, and antidepressants. History of only major depressive episode, diabetes, and social support as assessed by marital status were not significantly associated with incident CVD in this sample.

Table 4 shows the adjusted models for MHE, MDE, and manic symptom count as predictors of CVD. History of major depressive episodes were adjusted for in all models where MHE or manic symptom count was the main predictor variable. After adjusting for age, hypertension, smoking, and use of any psychotropic medication, history of manic or hypomanic episodes was a significant risk factor (OR: 2.97; 95% CI: 1.40, 6.34) for incident MI and CHF at 11.5 year follow-up. Odds of incident CVD were higher for MHEs than for MDEs after adjusting for demographic, medical, behavioral, and medication risk factors, but the relationship was not statistically significant. Manic symptom count was a significant risk factor for incident CVD at follow-up after adjusting for all risk factor variables.

Discussion

This study supports previous reports of association between BPD and CVD and extends the potential relationship to focus on the longitudinal association between mania, hypomania and incident CVD among community dwelling persons. A history of manic or hypomanic episodes was associated with odds of incident CVD 2.5–3 times higher than the odds among individuals with no history of manic, hypomanic, or depressive episodes, and odds of incident CVD 1.5–2.18 times that of individuals with a history of only major depressive episodes. In addition, the association between manic symptom count at baseline and incident CVD at 11.5 year follow-up suggests a possible dose-dependent relationship and further supports the longitudinal relationship between manic symptoms and incident CVD.

The explanation as to why MHEs are more at risk for CVD is likely to be multifactorial. Increased severity of illness, worse treatment outcome, and less time spent in recovered state are associated with negative health behaviors in BPD (Berk, et al, 2008; Dalton, et al, 2003; Goldberg, et al, 1999; Levin and Hennessy, 2004; Vanable, et al, 2003; Weiss, et al, 2005). Elevated levels of smoking have been associated with bipolar disorder and have been reported to increase with severity of mental illness (Venable, et al, 2003). Smoking has also been correlated with worse treatment outcome in acutely manic patients (Berk, et al, 2008). As in previous studies, smoking in this study was highest in MHEs. Also, in our study, participants with history of mania or hypomania were more likely to have comorbid history of alcohol abuse or dependence. This is consistent with two other large, population based studies where individuals with mania were six (Helzer, 1988; Helzer and Pryzbeck, 1988) and eight (Kessler, et al, 1996; Kessler, et al, 1997) times more likely to have substance use disorders than the general population. The impact of smoking and substance abuse or dependence on manic and hypomanic individuals may contribute to higher risk of CVD in this population (Schoppet and Maisch, 2001; Stefanatou, 2008). However, adjusting for

smoking or alcohol abuse/dependence the odds of CVD in MHEs remained the same. This could indicate that these behaviors, in addition to their known direct cardiopathic effect, indirectly increase the risk by contributing to more prevalent, severe and prolonged manic episodes.

Cardiovascular risk factors could be mediators or effect-modifiers in the longitudinal relationship between mania or hypomania and incident CVD. Higher prevalence of diabetes (Beyer, et al, 2005; McIntyre, et al, 2005; Regenold, et al, 2002) and hypertension (Beyer, et al, 2005; Johannessen, et al, 2006; McIntyre, et al, 2006) have been observed in patients with both BPD and depression. Weight gain, over weight and obesity (Keck and McElroy, 2003; Morriss and Mohammed, 2005), and metabolic disorder (Beyer, et al, 2005; Fagioli, et al, 2005) are other common comorbid medical conditions in BPD. While higher prevalence of neither diabetes nor hypertension was observed in our sample, other metabolic risk factors (e.g hypercholesterolemia) not measured in our study could contribute to the increased odds of CVD in MHEs.

A third possible explanation for higher odds of CVD in MHEs is the use of psychotropic medications. We found an association between CVD and typical antipsychotics, antidepressants, and lithium. Because this association existed in all three types of psychotropic medications as opposed to a specific class of medication, it is more likely that the relationship reflects treatment of an underlying condition, such as mania, rather than a direct cardiotoxic effect (Pratt, et al, 1996; Thorogood, et al, 1992). Furthermore, the potential side effects of psychotropic medications (i.e. obesity and diabetes) which are risk factors for cardiovascular disease were not observed in this sample, suggesting that it is the effects of mania, not the effects of medications, that is increasing the risk of incident CVD.

A final explanation for increased odds of CVD in the manic and hypomanic population is that MHEs may be more biologically vulnerable. Manic and depressed patients are more vulnerable to mental stress. Physiologic changes including elevated cortisol in response to stress has been found in manic subjects as well as in depressed subjects (Cassidy, et al, 1998; Schmitter, et al, 1995). Chronic over activation of pathophysiologically mediated stress response may contribute to atherosclerosis inducing states and mechanisms, including hypercorisolemia, pituitary adrenal gland enlargement, and increased hypothalamic corticotrophic-releasing factor (Musselman, et al, 1998). These abnormal physiologic responses to psychological stress may put manic patients at heightened risk of developing CVD.

Biological vulnerability is a potential explanation for the finding from this study was the MHEs were five years younger than MDEs and nine years younger than NMEs. This was unexpected as older age is among the most significant predictors of CVD (American Heart Association, 2008). However, it has been hypothesized inability to mediate stress response leads to chronic overactivity (i.e. "allostatic load") of organs and tissues involved in the physiologic response (McEwen, 2002). These systems, of which the cardiovascular system is included, experience excessive use which expedites the aging process (McEwen, 2002). Hypothetically, these physiological abnormalities could lead to exacerbation or development of cardiovascular disease. When examining only subjects in this study who had experienced a cardiovascular event, the age discrepancy was even more pronounced. MHEs were eleven years younger than MDEs and twenty years younger than NMEs. This is consistent with findings from a VA study where bipolar subjects with CVD were significantly younger compared to the general VA population (Kilbourne, et al, 2004). The physiological impact of labile mood and heightened affective states expedites the aging process, making manic, hypomanic, and bipolar individuals more prone to develop CVD and more vulnerable at a younger age (McEwen, 2002).

There are several limitations to this study. Due to the low prevalence of mania and hypomania, our study sample size was small and subsequently the number of incident CVD was also small. Also, 37.3% of MHEs had comorbid MDE. While we adjusted for history of MDE in our study, it is still possible that comorbid mild depression may have contributed to the increased risk of CVD among MHEs. Nevertheless, it is notable that MHE is associated with higher risk of incident CVD than depressive episode alone. Most epidemiological studies assess depressive symptoms only. Our study results suggest the need for assessment for manic symptoms in future epidemiological studies.

Studies have shown elevated CVD related mortality in bipolar individuals compared to the general population and to those with major depression (Angst, et al, 2002; Osby, et al, 2001). Examining only non fatal incidence is a conservative ascertainment of CVD, failing to account for more severe incidents. Future prospective studies should extend to look at fatal as well as non fatal CVD.

Finally, the sample of participants with a history of manic episodes and major depressive episodes was based upon DIS symptom criterion at wave I and II. Often, bipolar disorder initially presents itself in depressive episodes (Akiskal, et al, 1995; Bhugra and Flick, 2005), leading to misdiagnosis of major depression. Later presentation of mania or hypomanic (e.g. “switching over” to bipolar disorder (Akiskal, et al, 1995), could not be detected. New onset of manic or hypomanic episodes or major depressive disorder also could not be detected. Presence of manic symptoms was not assessed in Wave III; therefore, it was not possible to account for onset of manic episodes in other groups.

The summation of the limitations in this study suggests an under-ascertainment of participants with history of affective disorders, which is an important consideration when evaluating the results of this study. Future studies should extend to look at fatal as well as non fatal CVD in a manic and hypomanic population excluding comorbid major depressive disorder.

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Table 1**Baseline Sociodemographic and Health Factors**

	Hx Manic or Hypomanic Episodes (N=58)	Hx Major Depressive Episodes (N=71)	No Hx Mood Episodes (N=1339)	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Age	43.1 (7.8)	48.1 (10.3)	52.1 (15.7)	>0.001, >0.001
Education	12.1 (2.8)	12.6 (2.8)	11.7 (2.8)	0.287, 0.315
	N (%)	N (%)	N (%)	Fischer's exact
Sex				0.192
Female	35 (60.3)	51 (71.8)	817 (61.0)	
Male	23 (39.7)	20 (28.2)	522 (39.0)	
Race				0.004
Caucasian	24 (41.4)	47 (66.2)	842 (62.9)	
Other	34 (58.6)	24 (33.8)	497 (37.1)	
Marital status				0.006
married	22 (37.9)	27 (38.0)	705 (52.7)	
Psychotropic Medication				
Lithium	4 (7.0)	1 (1.4)	5 (0.37)	>0.001
Typical antipsychotic	12 (20.7)	12 (16.9)	42 (3.14)	>0.001
Antidepressant (MAOI, TCA)	13 (26.0)	16 (23.2)	60 (4.81)	>0.001
Health Behavior				
Smoking (1+ pack/day)	31 (58.5)	33 (47.1)	507 (40.7)	0.024
Hx alcohol abuse or dependence	19 (39.6)	13 (20.6)	164 (14.7)	>0.001
Self health rating (fair to poor)	7 (15.2)	10 (14.9)	85 (7.35)	0.017
Medical				
Hx hypertension	15 (30.0)	17 (25.0)	316 (26.0)	0.802
Hx stroke	0	1 (1.49)	9 (0.75)	0.601
Hx Diabetes	2 (4.17)	1 (1.52)	64 (5.34)	0.504

Table 2

Cardiovascular Disease Incidence at 11.5 Year Follow-up

	Hx Manic or Hypomanic Episodes (N=58)	Hx Major Depressive Episodes (N=71)	No Hx Mood Episodes (N=1339)
	N (%)	N (%)	N (%)
MI	4	5	50
CHF	1	0	9
Total Incident CVD III	5 (8.77)	5 (7.14)	57 (4.27)

Table 3

Results of Univariate Logistic Regression: Correlates of incident CVD at 11.5 year follow-up

Variable	Odds- Ratio	95% confidence interval		p-value
age	1.04	1.03	1.05	<0.001
Sex	0.76	0.58	1	0.053
Marital	0.83	0.63	1.09	0.183
Education	0.85	0.81	0.89	<0.001
Any Psychotropic	3.03	2.01	4.56	<0.001
Lithium	6.79	2.71	17.01	<0.001
Antidepressant	2.95	1.82	4.76	<0.001
Typical Antipsychotic	2.76	1.62	4.68	<0.001
Good Health	0.35	0.24	0.5	<0.001
Smoking (1+ packs/day)	1.75	1.33	2.29	<0.001
Hypertension	2.66	2.01	3.5	<0.001
Diabetes	0.86	0.44	1.7	0.665
Alcohol Abuse/Dependence	1.74	1.42	2.43	0.001
Manic Symptom Count	1.24	1.13	1.35	<0.001
Manic or Hypomanic episodes	2.24	1.34	3.76	0.002
Major Depression	1.5	0.89	2.54	0.129

Table 4

Odds of Incident CVD in MHE, MDE, and Manic Symptom Count: Results of multivariate logistic regression

	Model 1	Model 2	Model 3	Model 4
	OR (CI), p-value	OR (CI), p-value	OR (CI), p-value	OR (CI), p-value
MHE*	2.68 (1.51, 4.76), 0.001	2.62 (1.42, 4.86), 0.002	2.50 (1.32, 4.73), 0.005	2.97 (1.40, 6.34), 0.005
MDE	2.10 (1.22, 3.59), 0.007	2.12 (1.23, 3.67), 0.007	2.07 (1.18, 3.62), 0.011	1.42 (0.71, 2.84), 0.325
MHE vs MDE	1.66 (0.804, 3.43), 0.171	1.54 (0.716, 3.32), 0.269	1.50 (0.689, 3.27), 0.307	2.18 (0.86, 5.53), 0.102
Manic Symptom Count*	1.28 (1.16, 1.41), <0.001	1.26 (1.14, 1.39), <0.001	1.17 (1.04, 1.32), 0.009	1.18 (1.04, 1.36), 0.012

Adjusted model variables:

1- age, gender, education, marital status

2- age, gender, education, Hx diabetes, Hx hypertension

3- age, gender, education, Hx hypertension, Hx alcohol abuse of dependence, smoking (1+ pack/day)

4- age, gender, education, Hx hypertension, smoking (1+ pack/day), ever used psychotropic drugs (lithium, TCAs or MAOIs, or typical antipsychotics)

*
- Hx major depressive episode