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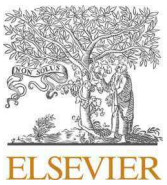

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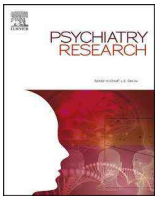

Comparative mortality risks in two independent bipolar cohorts

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ABSTRACT

Objectives: To compare mortality rates in bipolar disorder with common causes of mortality.
Methods: Observational data from the Prechter Longitudinal Study of Bipolar Disorder (PLS-BD) of 1128 participants including 281 controls was analyzed using logistical regression to quantify mortality rates in comparison with common comorbidities and causes of death. Outcome and treatment measures, including ASRM, GAD-7, PHQ-9 and medication use were used to stratify those with bipolar disorder (BD) that are alive or deceased. A larger cohort of 10,735 existing BD patients with 7,826 controls (no psychiatric diagnosis) from the University of Michigan Health (U-M Health) clinics was used as replication, observational secondary data analysis.
Results: The mortality rates are significantly different between those with BD and controls in both PLS-BD and U-M Health. Those with BD and are deceased have a higher percentage of elevated depression measures but show no difference in mania or anxiety measures nor medication use patterns. In both cohorts, a diagnosis of BD increases the odds of mortality greater than history of smoking or being older than $\geq$ 60-years of age.
Conclusion: BD was found to increase odds of mortality significantly and beyond that of a history of smoking. This finding was replicated in an independent sample.

1. Introduction

Bipolar disorder (BD) is a serious mental illness well known to be associated with premature mortality. Several studies have examined life expectancy and Years Per Life Lost (YPLL) for people with BD, and most suggest a 10–15 year reduction in lifespan and a markedly increased, 2–3 times risk of premature death in patients relative to the general population (Chan et al., 2021; Crump et al., 2013a; Kessing et al., 2015; Plana-Ripoll et al., 2020). This mortality gap between those with and without BD has persisted or even widened in recent decades despite an overall increase in life expectancy in the general population (Hayes et al., 2017; Lomholt et al., 2019; Staudt Hansen et al., 2019). From a public health perspective this suggests a combination of increasing risk factors, such as combined mental illnesses, and / or decreasing of protective factors and warrants further investigation and a compelling call for action (Ivbijaro, 2017).

The early mortality seen in those with BD was previously attributed to unnatural causes such as suicide, homicide and comorbid conditions such as substance abuse compared with the general population (Chan et al., 2021; Crump et al., 2013b; Hayes et al., 2015). However, the increased risk of early mortality in those with BD is also recognized to be related to the elevated prevalence and early manifestation of comorbid illnesses, particularly cardiovascular, metabolic and respiratory diseases (Chan et al., 2021; Crump et al., 2013b; Dragioti et al., 2023; Hayes et al., 2017; Henriques et al., 2022; Medici et al., 2015; Yin et al., 2022). Further, contributing factors driving the susceptibility of medical burden among BD individuals are believed to include the high frequency of modifiable negative health behaviors, such as cigarette smoking (Jackson et al., 2015; Lasser et al., 2000), a sedentary lifestyle (Vancampfort et al., 2016), poor eating habits, alcohol and other drug use, psychotropic medication-induced metabolic side-effects (Correll et al., 2015), and inequitable medical care (Heiberg et al., 2020). Among those with serious mental illness smoking is highly prevalent and up to 70 % of people living with BD smoke, which is far higher than the worldwide average of $<$ 20 % (Frye et al., 2013; Jackson et al., 2015; Lasser et al., 2000). Further, tobacco smoking was found to be a strong predictor of natural death in a dose dependent manner in those with schizophrenia, BD and major depressive disorder (Dickerson et al., 2021).

Additionally, and possibly confounding, are the use of psychotropic medications that also have adverse effects that contribute to general

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medical conditions, such as abnormal thyroid function, chronic renal disease, diabetes mellitus and elevated low-density lipoprotein cholesterol levels, all features of metabolic syndrome and (Correll et al., 2015; Gitlin, 2016; Grootens et al., 2018; Newcomer, 2009; Torrent et al., 2008) and all contributing to increased mortality risk factors.

The health inequalities experienced by people with BD, and other mental illnesses, represent a serious public health challenge that warrants urgent attention because of the high impact on health care utilization, societal costs, and premature death (Chan et al., 2021; Leboyer et al., 2022). Thus, a comprehensive evaluation of premature mortality patterns associated with BD is crucial for developing effective strategies and optimizing healthcare service delivery aimed towards reduction of avoidable deaths in this and other vulnerable populations (Liu et al., 2017). The comparison of a major behavior risk factor such as smoking concomitant with BD is important as it provides a perspective of the relative risks associated with the diagnosis and behavior in context of other comorbidities (Dickerson et al., 2021) and is a primary objective of this study. While the knowledge of high mortality rates among BD are now well known, identifying, and shaping modifiable behaviors among those living with BD and other mental illnesses has lagged. The final consideration of this study is the replication crisis in mental health research (Hicks, 2023) and to advocate for a study design that includes a strategy to validate the findings in an independent dataset, publish detailed methods and analysis code in an open and transparent manner (Stevens, 2017).

While the high relative mortality rates have been replicated elsewhere, herein we compare the odds of mortality in those with and without BD to other behavioral, medical, and physical comorbidities in both a well characterized research cohort and a larger population seen in a large tertiary medical center. We examined several comorbidities with direct relation to modifiable negative behaviors for an association to mortality in those with BD in these two independent samples from the same geographical region. Finally, we set the stage for strategic discussions around premature mortality in BD and highlight the need for a deeper understanding of root causes and establishing public health policies related to interventions.

2. Material and methods

The prospective PLS-BD longitudinal study was approved by the University of Michigan IRB HUM00000606 and all participants provided written informed consent and receive an annual stipend for participation. There were no additional incentives offered for participation in this specific, secondary data analysis study. Use of the U-M Health EHR as a secondary use of data was approved by IRB HUM00220353. This study followed the reporting requirements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline statement.

2.1. Participants

2.1.1. PLS-BD cohort

Participants from the Heinz C Prechter Bipolar Longitudinal Study of BD (PLS-BD) (Yocum et al., 2023), an observational and open cohort study that recruits individuals with BD and controls at the University of Michigan (U-M) were the initial test cohort. In this original study, participants were opportunistically recruited through media advertisements, outpatient and inpatient services, community outreach events beginning in 2006 and with rolling enrollment continuing until present. At study entry, all PLS-BD participants were evaluated using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and a Best Estimate process used by at least two doctorate level clinicians to confirm diagnoses using DSM-IV criteria. Participants were excluded if they had active/current substance abuse (per DSM-IV criteria) at enrollment or neurological disease. Controls were included if they had no history of DSM-IV axis I psychiatric illness and no family history of psychiatric diagnosis.

At the time of analysis, the secondary use of the PLS-BD cohort data included 1128 participants, 64 % female, 82 % reporting as Caucasian and 7 % as Hispanic or Latino, with an average age of 51 (min = 25, max = 95) years in 2023. Participants, 75 % ($n = 847$), have been diagnosed with Bipolar I, Bipolar II, Bipolar, NOS, or Schizoaffective Bipolar with the remaining 25 % ($n = 281$) as psychiatrically unaffected or psychiatric controls. Of the 1128 participants included in this study, 56 (5%) were deceased. Additional demographics information is provided in Table 1a. For current descriptive statistics regarding the PLS-BD, including attrition (withdrawn, non-continuing and lost-to follow-up, refer to (Yocum et al., 2023).

2.1.2. U-M health cohort

The replication sample, the U-M Health cohort, is a secondary data analysis cohort, drawn from all clinical services of U-M Health between January 1, 2019, to December 31, 2019. All patients with any BD diagnoses in the medical record were included. The control group was selected randomly in the database, i.e., there was no targeting of patients regarding demographics, nor care provider, but the patient had to have received care in a primary care setting anywhere in the enterprise health system in 2019. Inclusion in the control group required that the patient had no documented history of DSM-IV axis I psychiatric illness and no encounter within the University of Michigan hospitals with a complaint of depression nor anxiety. The study cohort included: 1) 10,735 who were diagnosed with Bipolar I, Bipolar II, Bipolar, NOS, or Schizoaffective Bipolar, and 2) 7826 individuals selected from those receiving primary care at U-M Health during 2019. From the total of 18,561 study participants, 1164 (6.3%) were deceased. The age range of the study set was 18–79 years (average age 51) as of December 31, 2019. Additional demographics information is provided in Table 1b.

2.2. Data measures and transformation

2.2.1. PLS-BD cohort

All self-report measures for the PLS-BD were collected digitally using REDCap electronic data capture tools hosted at U-M. (Harris et al., 2009, 2019) REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Age of the participant was calculated using date of birth and then dichotomized to a binary classification, >/= 60 or 〈 60 years of age. Three variables for socioeconomic status were transformed to the following categories. Annual household income was reduced to three categories, 'low' </= 35,000, 'mid' 〉 35,000 and < 100,000, or 'high' >/= 100,000 dollars. Education was reduced to three categories, 'less than a high-school' diploma or Generalized Education Degree (GED), obtained 'high-school' diploma or equivalent, some college but no 4-year college degree, or obtained 4-year 'college' degree. Occupation was categorized as either 'gainfully employed', i.e., full-time employment (work, student, retired or home maker), 'part-time' (part-time employed or student) or 'unemployed' / unable to work. History of social behavior including history of smoking, drinking alcohol, and use of illicit substances were obtained through self-report to clinician. Dichotomization of substance abuse or dependence was only indicated if diagnosed by clinician during the eDIGS and Best Estimates procedure. Comorbidities, body mass index (BMI), and prescription medicine use was provided as self-report. Mortality was captured through The State of Michigan Vital Records Department Death Certificate.

The Altman Severity Rating for Mania (ASRM) is a 5-item self-assessment questionnaire used in assessing the presence and severity of manic or hypomanic symptoms (Altman et al., 1997). The ASRM

Table 1
Demographics for the PLS-BD (a) and UM Health (b) cohorts under study. *P*-value is calculated between healthy control and BD with either two-sample *t*-test or Pearson's Chi-square depending on numeric (Age) or categorical variables (status, sex, race, BMI or smoking status).

a) PLS-BD	Undiagnosed (*N* = 281)	Bipolar (*N* = 847)	Overall (*N* = 1128)	*P*-value
Status				<0.001
Alive	279 (99.3 %)	793 (93.6 %)	1072 (95.0 %)	
Deceased	2 (0.7 %)	54 (6.4 %)	56 (5.0 %)	
Age				<0.001
Mean (SD)	47.9 (15.3)	52.0 (14.0)	51.0 (14.4)	
Median [Min, Max]	43.0 [26.0, 89.0]	50.0 [25.0, 95.0]	49.0 [25.0, 95.0]	
Sex				0.487
Male	106 (37.7 %)	297 (35.1 %)	403 (35.7 %)	
Female	175 (62.3 %)	547 (64.6 %)	722 (64.0 %)	
Missing	0 (0 %)	3 (0.4 %)	3 (0.3 %)	
BMI				<0.001
Normal	137 (48.8 %)	250 (29.5 %)	387 (34.3 %)	
Overweight	89 (31.7 %)	245 (28.9 %)	334 (29.6 %)	
Obese	54 (19.2 %)	347 (41.0 %)	401 (35.5 %)	
Missing	1 (0.4 %)	5 (0.6 %)	6 (0.5 %)	
Race				<0.001
Caucasian	202 (71.9 %)	725 (85.6 %)	927 (82.2 %)	
Not Caucasian	76 (27.0 %)	110 (13.0 %)	186 (16.5 %)	
Missing	3 (1.1 %)	12 (1.4 %)	15 (1.3 %)	
Ever Smoker				<0.001
No	245 (87.2 %)	507 (59.9 %)	752 (66.7 %)	
Yes	21 (7.5 %)	265 (31.3 %)	286 (25.4 %)	
Missing	15 (5.3 %)	75 (8.9 %)	90 (8.0 %)	
Income				<0.001
High	70 (24.9 %)	115 (13.6 %)	185 (16.4 %)	
Low	14 (5.0 %)	129 (15.2 %)	143 (12.7 %)	
Mid	96 (34.2 %)	150 (17.7 %)	246 (21.8 %)	
Missing	101 (35.9 %)	453 (53.5 %)	554 (49.1 %)	
Education				0.00133
College	157 (55.9 %)	293 (34.6 %)	450 (39.9 %)	
HS	23 (8.2 %)	94 (11.1 %)	117 (10.4 %)	
Less than HS	0 (0 %)	7 (0.8 %)	7 (0.6 %)	
Missing	101 (35.9 %)	453 (53.5 %)	554 (49.1 %)	
Employment				<0.001
Gainfully Employed	140 (49.8 %)	222 (26.2 %)	362 (32.1 %)	
Part-Time Employed	20 (7.1 %)	48 (5.7 %)	68 (6.0 %)	
Unemployed	20 (7.1 %)	124 (14.6 %)	144 (12.8 %)	
Missing	101 (35.9 %)	453 (53.5 %)	554 (49.1 %)	

b) U-M Health	Undiagnosed (*N* = 7826)	Bipolar (*N* = 10,735)	Overall (*N* = 18,561)	
Status				<0.001
Alive	7603 (97.2 %)	9794 (91.2 %)	17,397 (93.7 %)	
Deceased	223 (2.8 %)	941 (8.8 %)	1164 (6.3 %)	
Age				<0.001
Mean (SD)	56.5 (14.6)	47.3 (16.1)	51.2 (16.1)	
Median [Min, Max]	59.0 [22.0, 79.0]	47.0 [18.0, 79.0]	53.0 [18.0, 79.0]	
Sex				<0.001
Male	4276 (54.6 %)	3702 (34.5 %)	7978 (43.0 %)	
Female	3550 (45.4 %)	7033 (65.5 %)	10,583 (57.0 %)	
BMI				<0.001
Normal	1567 (20.0 %)	1771 (16.5 %)	3338 (18.0 %)	
Overweight	2336 (29.8 %)	1824 (17.0 %)	4160 (22.4 %)	
Obese	2938 (37.5 %)	3906 (36.4 %)	6844 (36.9 %)	
Missing	985 (12.6 %)	3234 (30.1 %)	4219 (22.7 %)	
Race				<0.001
Caucasian	5860 (74.9 %)	8670 (80.8 %)	14,530 (78.3 %)	
Not Caucasian	1944 (24.8 %)	2006 (18.7 %)	3950 (21.3 %)	
Missing	22 (0.3 %)	59 (0.5 %)	81 (0.4 %)	
Ever Smoker				<0.001
No	4773 (61.0 %)	3184 (29.7 %)	7957 (42.9 %)	
Yes	2299 (29.4 %)	5047 (47.0 %)	7346 (39.6 %)	
Missing	754 (9.6 %)	2504 (23.3 %)	3258 (17.6 %)	
Alcohol Abuse				<0.001
No	7582 (96.9 %)	9065 (84.4 %)	16,647 (89.7 %)	
Yes	244 (3.1 %)	1670 (15.6 %)	1914 (10.3 %)	
Sleep Apnea				<0.001
No	6607 (84.4 %)	9504 (88.5 %)	16,111 (86.8 %)	
Yes	1219 (15.6 %)	1231 (11.5 %)	2450 (13.2 %)	

*Body Mass Index (BMI).

5-item is scored consistent with DSM-IV criteria and summed for a total score per measurement. The Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) is a self-administered module to measure depression, which scores each of the 9 DSM-IV criteria as "0″ (not at all) to "3″ (nearly every day). These responses are summed for a total score per measurement (Kroenke et al., 2001). The Generalized Anxiety Disorder Scale (GAD-7) is a self-administered instrument to measure severity and screen for the four most common anxiety disorders; Generalized Anxiety Disorder, Panic Disorder, Social Phobia and Post Traumatic Stress Disorder (Spitzer et al., 2006). The GAD-7 assigns scores of 0, 1, 2, and 3 to the response categories "not at all," "several days," "more than half the days," and "nearly every day," respectively. These responses are also summed for a total score.

For each mood measure, a proportion of the number of elevated observations out of the total number of observations for each participant was calculated. An elevated observation was considered a score of >/= 6 on the ASRM, >5 of the PHQ-9 and >/= 10 on the GAD-7. Then, if a participant had a proportion of elevated measures greater than the median of all proportions for those with bipolar diagnosis, this participant was considered as having chronically elevated symptom measures. This method condensed the symptom measures into binary bins, having or not having chronically elevated mood symptom measures, allowing to both normalize the symptom measures over the number of observations per participant and be able to inter-compare all mood symptom measures.

Pharmaceutical compliance is measured in the PLS-BD by yearly self-report. Every pharmaceutical agent is recorded as self-reported and later harmonized with the NIH National Library of Medicine RxNorm ingredient name and RxCUIDs (Peters, 2008). These RxCUIDs were harmonized to VA Class codes for the six psychotropic classes; anticonvulsants, antipsychotics, antidepressants, sedatives, stimulates and separately lithium, as a mood stabilizer, was extracted (Winnenburg and Bodenreider, 2014). To compare psychotropic class use between living status in those with BD in the PLS-BD cohort, a normalized value for each participant was created. This normalized value calculated the number of years a participant reported to be on an agent in that psychotropic class divided by the total number of years that participant was in the study. Additionally, the total number of psychotropic agents is

normalized similarly, i.e., the total number psychotropic agents reported each year is summed and divided by the number years in study. Both metrics allow for each participant to have comparable number of years on pharmaceuticals.

2.2.2. U-M health cohort

The retrospective collection of the electronic health record (EHR) data for U-M Health cohort was accessed via DataDirect (https://datadirect.med.umich.edu/), an electronic data repository of the Michigan Health Care System. DataDirect is a self-service tool enabling access to the structured clinical data of diagnoses, encounters, procedures, medications (order and administered), and laboratory values on over 5 million patients from across the U-M Health enterprise. History of social behavior including history of smoking, drinking alcohol, and use of illicit substances were obtained through self-report to clinician. Age of the participant was calculated using date of birth and then dichotomized to a binary classification, >/= 60 or < 60 years of age. Binary categorization of substance abuse or dependence was only considered if diagnosed by clinician with ICD-9 codes. Comorbidities, BMI, and diagnoses was provided by clinician. To be diagnosed with sleep apnea, the patient much have one of the following ICD-9 codes: "327.21", "327.22", "327.23", "768.04", "327.27". All pharmaceutical agents, either prescribed or administered is captured as RxCUIDs and harmonized to VA Class codes as completed in the PLS-BD cohort. Mortality was captured through The State of Michigan Vital Records Department Death Certificate. Socioeconomic variables at the patient level were unable to be obtained.

2.3. Statistical analysis

Analyses were completed using the R software (https://cran.r-project.org/) (v4.2.0:: Vigorous Calisthenics) using packages dplyr (v1.0.9), lubridate (1.8.0), data.table (v1.14.2), jtools (v2.2.0) and stats (v4.2.0) for analysis and ggplot2 (v3.3.6), sjlabelled (v1.2.0), sjPlot (v2.8.10) for visualizations. All analysis scripts used in this project are available in an open and transparent manner.

Descriptive statistics are provided for both PLS-BD and U-M Health cohorts using either a two-sample Fisher Exact, Student's T-test or a Pearson's Chi-square depending on numeric (age) or categorical variables (mortality status, sex, race, BMI bins, or smoking status, diagnosis of sleep apnea, diagnosis of alcohol abuse, income bins, employment bins and educational bins), (Table 1). Fisher Exact test was used to described significance between those alive and deceased in the PLS-BD comorbidity (Fig. 1), outcome mood measures (Table 2), and normalized years on psychotropic medications (Fig. 3). Generalized linear models (stats::glm) using the binomial link family was used for all regression analyses with the objective to quantify the relative risk of mortality between different variables. In the PLS-BD cohort, the mortality response variable was used with predictor binary variables of BD diagnosis, sex, non-Caucasian, binned age, categorized BMI, smoking history, substance abuse history, comorbidity of asthma, diabetes, and high-blood pressure (Fig. 2). In the U-M Health cohort, again generalized linear models with a binomial link family was used with the response variable of mortality with binary variables of BD diagnosis, sex, non-Caucasian, binned age, categorized BMI, history of smoking, alcohol and substance abuse, comorbidity of diabetes, high-blood pressure, depression, sleep apnea and psychoses (Table 3). In all regression models, missing values is handled by omission; that is observations are removed if they contain any missing values in the regression model variables.

Table 2
Mood survey characteristics of those alive or decease with BD in the PLS-BD. Percent high is defined as the percentage of measurements above a threshold ($\geq$ 6 for the ASRM, $\geq$ 5 for the PHQ-9 and $\geq$ 10 for the GAD-7) over the total number of measurements per participant.

Prechter Longitudinal	Alive (N = 793)	Deceased (N = 54)	P-value
% High ASRM			
Mean (SD)	19.1 (24.0)	21.5 (26.3)	0.562
Median [Min, Max]	10.0 [0, 100]	10.5 [0, 100]	
% High PHQ-9			
Mean (SD)	62.0 (35.3)	72.9 (35.0)	0.012
Median [Min, Max]	70.0 [0, 100]	92.5 [0, 100]	
% High GAD-7			
Mean (SD)	24.8 (31.6)	29.2 (38.1)	0.122
Median [Min, Max]	8.00 [0, 100]	0 [0, 100]	

* *Altman Self-Rating Mania Scale (ASRM); Patient Health Questionairre 9-questions (PHQ-9); Generalized Anxiety Disorder 7-questions (GAD-7).*

3. Results

Table 1 (a) and (b) shows the number of study participants and sociodemographic characteristics for the two cohorts studied: a) PLS-BD study (n = 1182) and b) The U-M Health patient population (n = 18,561).

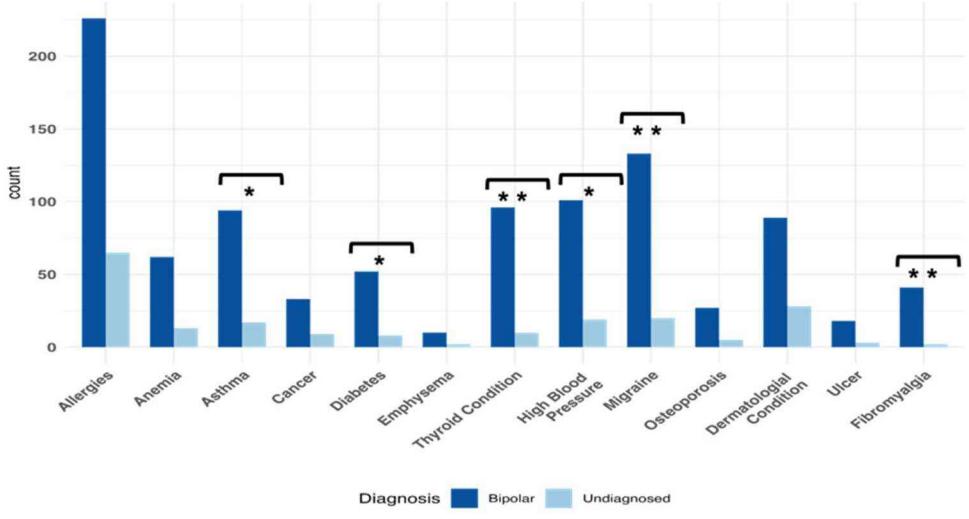

Fig. 1. Medical comorbidities for those with BD or undiagnosed psychiatric control in the PLS-BD. * p-value < 0.05, ** p-value < 0.001.

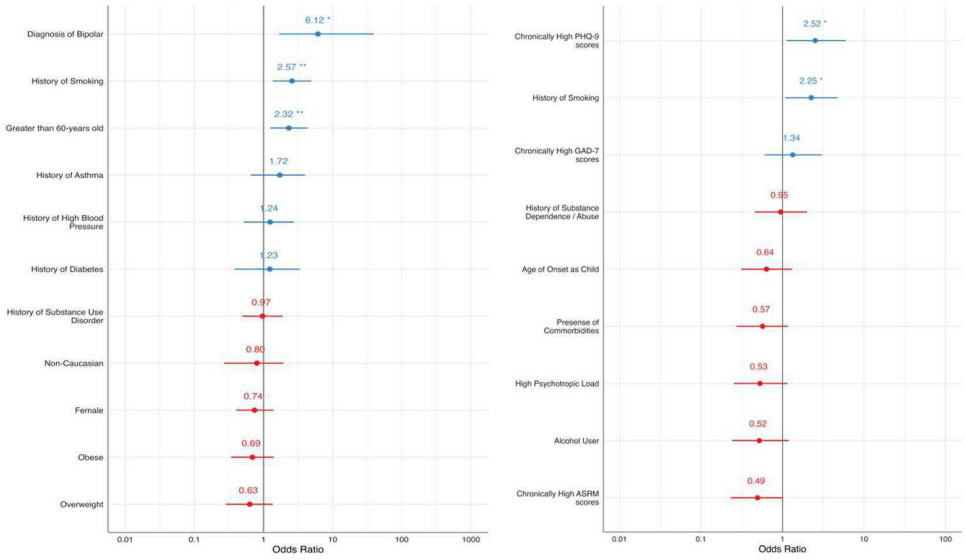

Fig. 2. Logistic regression results in the PLS-BD. *(a)* shows the adjusted odds ratio of mortality for those diagnosed with BD and several medical comorbidities. *(b)* shows the adjusted odds ratio of mortality for only those diagnosed with BD. * *Altman Self-Rating Mania Scale (ASRM); Patient Health Questionairre 9-questions (PHQ-9); Generalized Anxiety Disorder 7-questions (GAD-7).*

Table 3
Logistic regression results for mortality in the U-M Health cohort. *(a)* shows the results for those diagnosed with BD and several medical comorbidities. *(b)* shows the results for only those diagnosed with BD.

Coeffcient	(a) *Odds-Ratio*	*Conf. Int (95 %)*	*P-Value*	(b) *Odd-Ratio*	*Conf. Int (95 %)*	*P-Value*
Diagnosis of Bipolar Disorder	4.35	3.43 – 5.53	<0.001			
Greater than 60-years old	3.02	2.56 – 3.57	<0.001	2.85	2.38 – 3.42	<0.001
Female	0.78	0.67 – 0.91	0.002	0.75	0.62 – 0.89	0.001
Non-Caucasian	0.87	0.71 – 1.06	0.182	0.75	0.59 – 0.95	0.019
Obese	1.02	0.83 – 1.26	0.85	1.02	0.81 – 1.29	0.866
Overweight	0.82	0.65 – 1.04	0.103	0.86	0.66 – 1.12	0.262
History of High Blood Pressure	5.12	4.29 – 6.11	<0.001	4.85	3.94 – 5.97	<0.001
History of Diabetes	1.85	1.54 – 2.22	<0.001	1.84	1.48 – 2.29	<0.001
History of Smoking	1.95	1.64 – 2.32	<0.001	1.85	1.51 – 2.27	<0.001
History of Sleep Apnea	0.83	0.68 – 1.01	0.06	0.79	0.62 – 1.00	0.052
History of Alcohol Abuse	1.74	1.42 – 2.13	<0.001	1.63	1.31 – 2.03	<0.001
History of Depression	0.81	0.66 – 0.99	0.039	0.79	0.64 – 0.98	0.028
History of Subtance Dependence / Abuse	1.21	1.00 – 1.47	0.051	1.2	0.98 – 1.47	0.078
History of Psychoses	1.21	1.00 – 1.47	0.053	1.24	1.02 – 1.51	0.033
Observations	14,037			7381		
R^2 Tjur	0.139			0.133		

3.1. PLS-BD: initial test cohort analyses

An initial descriptive statistical comparison of participants in the PLS-BD cohort (Table 1a) show a significant difference in mortality between bipolar (6.4%) and psychiatrically unaffected controls (0.7 %) (p-value < 0.001). There was also a difference in age (p-value < 0.001), BMI (p-value < 0.001), race (p-value < 0.001), smoking status (p-value < 0.001), income (p-value < 0.001), education (p-value = 0.001), and employment (p-value < 0.001) in the PLS-BD cohort between those with and without bipolar disorder.

An investigation into comorbidities comparison between bipolar and controls in the PLS-BD cohort showed a significant difference in the history of asthma (p-value = 0.015), diabetes (p-value = 0.032), thyroid condition (p-value < 0.001), high blood pressure (p-value = 0.014), migraine (p-value < 0.001) and fibromyalgia (p-value < 0.001). Differences in allergies, anemia, cancer, emphysema, osteoporosis, dermatological conditions, ulcers were not found to be significantly different between those with bipolar and control, shown in Fig. 1. There were no cases of liver conditions nor epilepsy in the control group with 25 and 19 cases in the bipolar group, respectively.

In the PLS-BD, the ASRM, GAD-7, PHQ-9, were surveyed every other month with a mean of 30 [range: 1 – 92] measurements for the ASRM, a mean of 29 [range: 1–92] measurements for the PHQ-9 and mean of 23 [range: 1–58] GAD-7 measurements. There was no difference between deceased and living in those with bipolar disorder in the PLS-BD cohort for percentage of elevated ASRM or GAD scores. There was a significant difference between the deceased and living in percentage of elevated PHQ-9 scores, 72.9 % in the deceased vs. 62 % in the living (p-value = 0.01), shown in Table 2.

Logistic regression was completed using the response variable of living status (alive or deceased) in the PLS-BD cohort. Shown in Fig. 2a, a diagnosis of bipolar increases the mortality (odds-ratio = 6.12, p-value = 0.018) greater than a history of smoking (odds-ratio = 2.57, p-value = 0.004), and being older than 60-years of age (odds-ratio = 2.32, p-value = 0.008). There were no significant increases or decreases in mortality for being non-Caucasian, female, obese, overweight or a history of asthma, high blood pressure, diabetes, or substance use disorder. Examining the bipolar population alone in the PLS-BD cohort, shown in Fig. 2b, having high PHQ-9 scores (odds-ratio = 2.52, p-value = 0.03) and a history of smoking (odds-ratio = 2.25, p-value = 0.03) increased the mortality. There were no significant findings for chronically high GAD-7 scores, chronically high ASRM scores, history of substance dependence or abuse, alcohol use, age of onset of bipolar disorder, presence of comorbidities or high psychotropic load.

In those with bipolar, there was no statistical difference, between

those alive and those deceased, in the normalized years participants were on any of the six major classes of psychotropics (Fig. 3a), nor in the total number of normalized years the participants used any psychotropic medications (Fig. 3b).

3.2. U-M health; replication results

An initial comparison of participants in the U-M Health cohort show a significant difference in mortality between bipolar (8.8%) and undiagnosed controls (2.8%) (p-value < 0.001). There was also a difference in age (p-value < 0.001), BMI (p-value < 0.001), race (p-value < 0.001) and smoking status (p-value < 0.001) in the U-M Health cohort between those with and without bipolar disorder, Table 1b. Mood measures were not routinely captured and available for the U-M Health cohort.

Using the same logistic regression methodology, results shown in Table 3a, those patients with bipolar disorder in the U-M Health cohort show a significant increase in mortality with a odds-ratio = 4.35 (p-value < 0.001) compared with controls. This increased association was lower than a history of high blood pressure (odds-ratio = 5.12, p-value < 0.001), but higher than diabetes (odds-ratio = 1.85, p-value < 0.001), older than 60-years of age (odds-ratio = 3.02, p-value < 0.001), history of smoking (odds-ratio = 1.95, p-value < 0.001), or alcohol abuse (odds-ratio = 1.74, p-value < 0.001). There was a slight, yet significant, decrease in mortality for being female (odds-ratio = 0.78, p-value = 0.002) and history of depression (odds-ratio = 0.81, p-value = 0.039). Being non-Caucasian, overweight, obese or a history of psychosis nor a diagnosis of sleep apnea was not found to be significant.

In the BD only subset (no additional comorbidities) of the U-M Health cohort (Table 3b), traditional comorbidities of greater age (odds-ratio = 2.85, p-value < 0.001), history of high blood pressure (odds-ratio = 4.85, p-value < 0.001), diabetes (odds-ratio = 1.84, p-value < 0.001), smoking (odds-ratio = 1.85, p-value < 0.001), and alcohol abuse (odds-ratio = 1.63, p-value < 0.001) increased the mortality. Being female (odds-ratio = 0.75, p-value = 0.001), and non-Caucasian (odds-ratio = 0.75, p-value = 0.019), decreased the mortality within the bipolar population in U-M Health.

4. Discussion

According to the CDC, the leading causes of death in 2021 does not include BD, nor any psychiatric illness (Leading Causes of Death: United States, 1999–2017. National Center for Health Statistics. 2019). The most recognized reported causes such as heart disease, cancer, stroke, Alzheimer's disease, chronic respiratory diseases, and diabetes have held these unenviable positions for decades. Understandably, causes of mortality are listed according to the immediate cause and often fail to identify the underlying causal syndrome(s). However, the focus on immediate causality has served to rally public health policy and intervention leading to public awareness of cardiovascular and metabolic disease risks emphasizing the importance of physical exercise, reducing smoking, and have resulted in food label changes. In mental health, an example of a public health policy is the adoption of the 988 Suicide and Crisis Lifeline in July 2022 (Suran, 2023). The impact of this new public health policy on mortality remains, as yet, unknown and may take years to fully assess. Given the complexity, comorbidities, and chronicity of mental health conditions, far more attention to policy is needed as the mortality is anticipated to remain high and the demand for care substantial. The complexity and severity are reflected here in two independent datasets that included the common causes of mortality and comorbidities in the regression models. Namely, and most importantly, having BD surpassed other medical conditions, except hypertension, as a primary underlying condition associated with premature mortality.

The causal factors behind the premature mortality in BD are compounded by the known link between comorbidities, such as the interrelated factors of metabolic syndrome (Giménez-Palomo et al., 2022) which have a common etiology including shared genetic susceptibility (Amare et al., 2017) and overlapping pathophysiological mechanisms, e.g. inflammatory dysregulation (SayuriYamagata et al., 2017). Metabolic syndrome is highly prevalent in those with BD (Vancampfort et al., 2013), in part due to shared common risk factors that include endocrine disturbances (Dragasek et al., 2023; Salvador et al., 2019), imbalance between sympathetic and parasympathetic autonomic nervous system (Ortiz et al., 2022). Also contributing are behaviors such as physical inactivity and overeating which are more commonly found in those with impaired executive functioning and decreased impulse control (Dalkner et al., 2021). In this research, we show afresh, the rates of obesity, smoking, alcohol abuse, and sleep apnea are significantly higher in those with than without BD.

Lifestyle patterns among many living with BD are often unfavorable and include a range of personal, social, and vocational challenges in addition to the above-mentioned diet, exercise, and substance use related difficulties. These data show a significant increase in the rates of lower educational levels, gainful employment with concomitant increases in unemployment and lower income levels. It has been reported that AUD co-occurs with BD with population-level lifetime estimates greater than 50 % (McIntyre et al., 2022). This estimate does not replicate in our U-M Health cohort, which found, while a significantly greater prevalence of AUD was identified in BD, only 16 % of those with BD were identified as having co-occurring AUD. This relatively low rate possibly reflects a lapse in the collection of lifetime history, especially if the individual did not meet criteria or reveal evidence of AUD during the medical encounter. The modifiable behavior, smoking is also known to

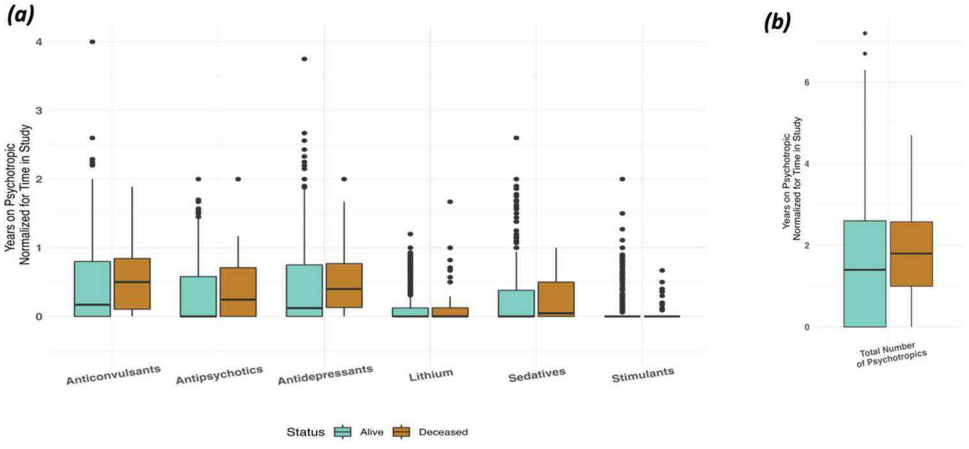

Fig. 3. In those with BD in the PLS-BD, there is no difference, between those alive and those deceased, in *(a)* normalized time participants are on any of the six major classes of psychotropics or the *(b)* total number of psychotropic medications.

be more common among those with BD (Lasser et al., 2000). This was also confirmed in the work described herein, those with BD have a history of smoking far more than the controls in both the test and replication datasets.

The importance of healthy lifestyle notwithstanding, it must be recognized that the hard facts surrounding the major causes of death have had a major impact on public policy and implementation of changes at the societal level. The best example being anti-smoking campaigns, policy, and legislation regulating public smoking have resulted in a significant population decrease in smoking. The current study finds that the adjusted mortality rates remain much higher for someone with BD than most of the common comorbidities listed as top leading causes of death, with the notable exception of high blood pressure. Remarkedly, having BD results in a rate of mortality much higher than a history of smoking or being greater than 60-years of age even after adjusting for race and sex in both cohorts. Other known associations remain, those with BD in our PLS-BD cohort, mortality is more significantly associated with a consistently high level of depression, however, not mania nor anxiety, nor having a higher number of years taking psychotropic medications. In both datasets, being female reduced the odds of mortality. This has been described as a sex advantage owed to favorable social and environmental determinants of health (Curtis and Han, 2021). Being non-Caucasian was also associated with reduced mortality in both cohorts. This may be reflective of the greater reductions and difference decrease of overall mortality in the last few decades for all non-Caucasians as compared to Caucasians (Hahn et al., 2018).

In the BD group of the UM Health replication cohort, there was a slight, yet significance decrease in mortality in those with a history of a depression diagnoses, which was not found in the PLS-BD cohort. In the U-M Health cohort there were no repeated measures of the PHQ-9 and it was not possible evaluate the chronic nature and burden of depression as was calculated in the PLS-BD cohort. However, consistent with other findings (Angst et al., 2002; Crump et al., 2013b; Kessing et al., 2015; Ösby et al., 2019), those with BD and were deceased in the UM Health replication cohort had a higher incidence of medical comorbidities including; alcohol abuse, diabetes and high blood pressure.

These findings herein were found in a prospectively studied longitudinal research cohort and then replicated in a large patient population at a tertiary medical center primarily substantiate others' work over the years with other large cohorts (Dragioti et al., 2023; Ivbijaro, 2017; Liu et al., 2017) namely, having a diagnosis of BD is a major risk of premature death and is associated with several medical and physical comorbidities that also present a risk of premature death. The salient point being that having BD outpaced other mortality risk factors, including the well-known risk factor of smoking. Further, in the prospective PLS-BD study, the self-report of ongoing, chronic depressive symptoms associated with a greater mortality risk than a comorbidity history of depression as seen in the U-M Health cohort.

A further methodological contribution of this report includes the demonstration of replicating the findings from a smaller and more detailed study in a much larger independent sample. Not all findings were replicated, e.g. hypertension, consistent with a complex set of contributing factors behind mortality; further clarification and study is needed in a population that is more diverse regarding race, ethnicity and socioeconomical status, along with high granularity of data. Specifically, the mood measures analysis, which found mortality associated with consistently high depression values were unable to be repeated in the U-M Health cohort due to the absence of these measures in the EHR. However, as collecting survey measures like the ASRM, GAD-7 and PHQ-9 has commenced as part of U-M Health system Patient Reported Outcome Measures (PROMs), more detailed analysis will be possible in future studies (Wong et al., 2022).

The limitations of the current report also include prior knowledge of the data without pre-registration of the study and represents a secondary data analysis. While hypothesis driven, the potential of inherent bias remains due to the authors deep knowledge of the data strengths and weaknesses. Additionally, the replication sample was not a prospective study with systematic collection of data, rather it was a clinical sample with information gathered in the course of clinical care. Unfortunately, there is considerable missingness in the clinical data specific to BMI and history of smoking in the UM-Health cohort and as such those observations with missingness were not included in the regression analyses. Further, Not all data variables can be directly compared due to the opportunistic collection of clinical data, also is a limitation of the replication aspect of the study. Additionally, both samples were in the limited geographical region of SE Michigan that serves a predominantly Caucasian demographic. Further, the variable frequency of mood measures is obscured by dichotomization technique in the analysis. The designation of 'chronically elevated' (vs. not) was done to reduce complexity of the analyses and increase the signal to noise ratio.

Call to Action: The finding that living with BD was a greater risk factor for early mortality than smoking tobacco, a globally recognized leading cause of death, was a major surprise. When including the spectrum of BD, it is estimated that 4 % of the population lives with BD. It is a chronic illness with increasing comorbidities over the lifetime of the individual. The impact of BD is profound, beginning in early life with the onset of illness that risk disrupting the personal, social, and vocational course of the individual, through the lifetime with accumulation of comorbidities and ongoing symptoms (depression) with consequences that not only compromise the quality of life but lead to early mortality.

What policies, programs, and societal changes can be implemented to both improve the quality of life as well as reduce mortality for those living with BD? This is a challenge with no easy or straightforward solutions, while medications clearly are important (Nestsiarovich et al., 2022; Ratheesh et al., 2023), there is a surge of interest in engagement of stakeholders, people and families living with BD as well as care providers, to identify and prioritize needs, programs, and policies in the care and management of BD (Madden et al., 2021). Fostering communication and active learning about community priorities is key to developing a rational strategy towards decreasing mortality in BD.

4.1. Significant outcomes

The increase in mortality for those living with BD was confirmed. In these two independent samples, the impact of BD on mortality surpassed that of common causes including smoking tobacco.

4.2. Limitations

This study was performed in a single geographic location with a homogenous ethnic and racial population however well matched between research and clinical cohorts. This study includes self-report surveys and may be influenced by respondent biases.

Data availability statement

Heinz C. Prechter Bipolar Research cohort data are available via request at [prechter-data-request@med.umich.edu] conditional on Data Use Agreement. Data can be shared in an itemized, flat file format or a data analyst may be available for collaboration who can provide aggregate summaries as demonstrated in other global collaborations. R code to produce results herein can be provided in a manner of open and transparent research upon request.

Ethics approval

The Heinz C. Prechter Bipolar Research Study is reviewed annually and approved by the University of Michigan Institutional Review Board, IRBMED, HUM0000606. All participants are provided written informed consent prior to enrollment in the study. A consent is reviewed with the participant annually for continuation in the study. Independently, the

IRBMED, HUM00220353, approved secondary use of the electronic medical record data for creation and study of the U-M Health cohort.

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CRediT authorship contribution statement

Anastasia K. Yocum: Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Visualization, Writing – review & editing. **Emily Friedman:** Formal analysis, Methodology. **Holli S. Bertram:** Project administration, Supervision. **Peisong Han:** Methodology, Supervision, Writing – review & editing. **Melvin G. McInnis:** Resources, Writing – review & editing, Funding acquisition, Project administration, Supervision.

Declaration of Competing Interest

MGM has consulted for Janssen and Otsuka Pharmaceuticals and received research support from Janssen. HJB serves on the scientific advisory board for Natrol, LLC, and Moving Mindz, Pty Ltd. All other authors report no conflicts related to this work.

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